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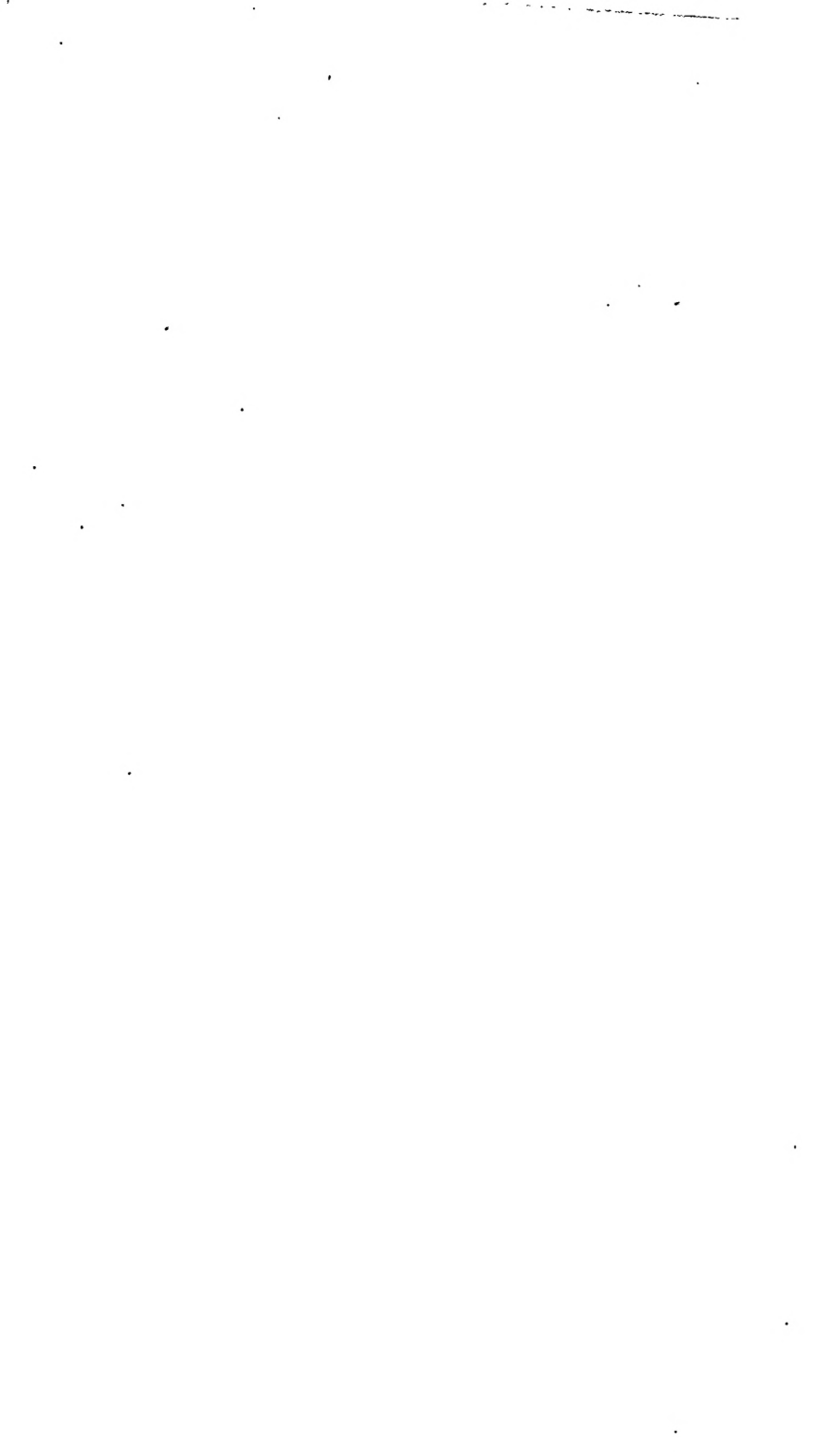
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THE MEDICAL CLINICS OF NORTH AMERICA

Volume 17

Number 1

CLINIC OF DR. LEWIS GREGORY COLE

NEW YORK CITY

HYPERTROPHIC GASTRITIS

A WELL-DEFINED group of pathologic findings constitutes a definite disease to which the term "hypertrophic gastritis" is applicable. We make this statement, in spite of the fact that many eminent pathologists maintain that there is no such lesion as hypertrophic gastritis.

The disease that is the subject of this communication is not a simple gastritis with slight changes in the mucosa, nor a catarrhal gastritis with an over-abundance of mucosa, nor that gastritis of Jagunski which has attracted so much attention during the last four or five years. Neither is it the atrophic gastritis described by one of the Cole Collaborators (Morse) in a symposium on this subject at the 1931 meeting of the American Roentgen Ray Society, nor is it the ulcerative gastritis described by this author in that symposium. It might be better, perhaps, to find a new name for this particular group of pathologic findings, but the old, discarded term, "hypertrophic gastritis," describes it so accurately that there seems to be no better choice.

In this lesion, hypertrophy is the keynote. The mucosa is both larger and thicker than normal. When this enlarged and thickened mucosa is thrown into folds or rugae that are very much larger than normal, they encroach upon the lumen. If the lesion occurs in the pyloric region, the enlarged rugae, running in all directions, almost obliterate the lumen of this region

entirely. In the corpus, where the diameter of the lumen of the stomach is much greater than at the pylorus, the diminution is not so evident.

The lesion is seen best in the living, functioning stomach at operation, where the edema and congestion of the organ are apparent both by inspection and palpation. This edema and congestion—such important factors in the pathologic process—diminish or disappear after death, of course, and diminish very materially even after removal of the surgical specimen. Hence, the surgical findings, as observed when the abdomen is first opened, are most important.

At the time of surgical exploration, before the pylorus is removed, the outside of the stomach has a peculiar appearance. The network of blood vessels on the surface of the stomach appears as a pattern of brilliant red lines against a pinkish white serosa. This may be the “red stomach” of Schumacher, although he speaks of the “red stomach” as being more of a “blush,” whereas this appearance reminds one of a girl in a white dress sitting in a brilliant, red cord hammock, the bright red network of cords corresponding to the blood vessels, the white dress to the serosa.

On palpation, the wall of the stomach in the involved region is much thicker than normal. It is much softer to the touch than when the thickening is caused by a neoplastic or even by an inflammatory infiltration.

In obtaining our surgical specimen, clamps were not employed, and when the gastric wall was cut the mucosa extruded from the cut surface in an uncanny manner, even more than normal; in normal cases, it often extrudes to such an extent that the surgeon is tempted to cut off the protruding edges. After the specimen was removed, the mucosa bore a strong resemblance to a bunch of “night walkers” (large angle-worms).

Pathologic Findings.—The large hypertrophied rugae in the pyloric region, as observed in the freshly removed surgical specimen, are two or three times the size of the normal rugae in this region. They are larger even than the normal rugae so often seen on the left border of the corpus, along the greater curva-

ture. These large hypertrophied rugae, which are characteristic of hypertrophic gastritis, may occur in any region of the stomach, but when they occur in the pyloric region they are of more clinical significance than elsewhere, because they give rise to more symptoms, particularly if they occur within the limits of the fan-shaped muscle. Such large, hypertrophied rugae in the pyloric region may run in all directions, that is, longitudinally, obliquely, and even transversely, but they have a very definite general tendency to run transversely or obliquely to the long

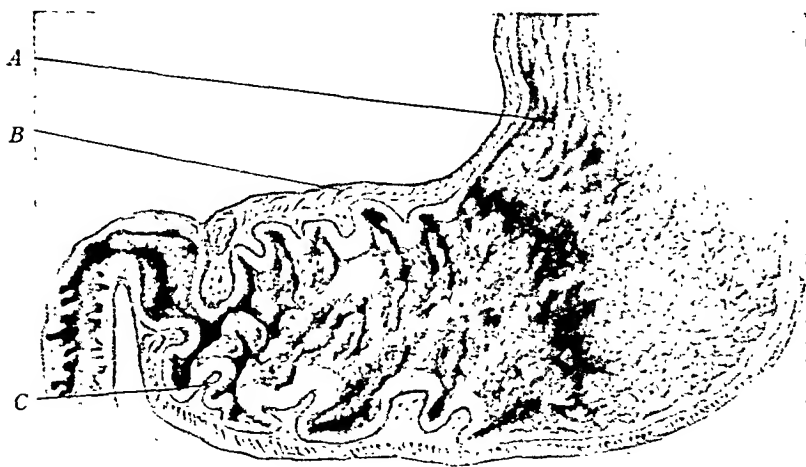


Fig. 1.—Hypertrophic gastritis with the lumen of the pyloric region filled with a bulky mass of mucosal folds. *A*, Normal stomach; *B*, muscularis propria; *C*, hypertrophied fold.

axis of the stomach. When these rugae in the pyloric region along the greater or lesser curvature are viewed in profile on cut section they cause the outline of the lumen to have a very ragged appearance. Deep sulci or crevices may be formed in between the large rugae. These hypertrophied rugae may be so large and numerous as to form a bulky mass which almost fills the pyloric end of the stomach, even though the muscular coat of the stomach is not diminished in diameter by spasmodic contraction of the muscular coat or by pressure from without.

Gross Appearance of the Inside of the Normal, Living, Functioning Stomach.—In order to appreciate the pathologic process just described, and in order to differentiate rugae that are characteristic of hypertrophic gastritis from normal rugae, one must have an accurate conception of the normal appearance of rugae or folds in the mucosa.

The mucosal coat of the stomach normally is much larger than the muscular coat except when the stomach is fully distended. Therefore, when the muscular coat is contracted and the lumen of the stomach is diminished in diameter and length, the mucosa, not having the power of contraction, is thrown into folds or rugae. These rugae have different characteristics in different regions of the stomach. Along the greater curvature, they are crinkled and run in all directions; along the lesser curvature, they are straight and run parallel with the lesser curvature, forming the so-called "gastric pathway." They are absent in the pyloric region when the antrum is fully expanded, but when it is compressed from without or when the pyloric canal is contracted by the fan-shaped muscle, rugae are present and usually run longitudinally, although they may run obliquely or transversely, but they are small compared with those observed in hypertrophic gastritis.

It is impossible, of course, to see the entire inside of the living functioning stomach, but, from an intensive study of serial roentgenograms, one comes to know the size and shape of the lumen as well as the size, shape, and distribution of the mucosal folds. From an intensive study of postmortem and surgical specimens prepared in a special manner, we have come to know the anatomical appearance of these folds on the inside of the dead stomach. By building around the lumen of the living stomach, as observed roentgenologically, the structures observed in the dead stomach, we have come to know the appearance of the inside of the living stomach. A drawing by Miss M. Fletcher, under the author's personal supervision, illustrates the appearance of the living, functioning stomach better than do illustrations in standard texts of anatomy. This drawing is reproduced as Fig. 2. With it one may compare

Fig. 1, a drawing similarly made of a case of hypertrophic gastritis.

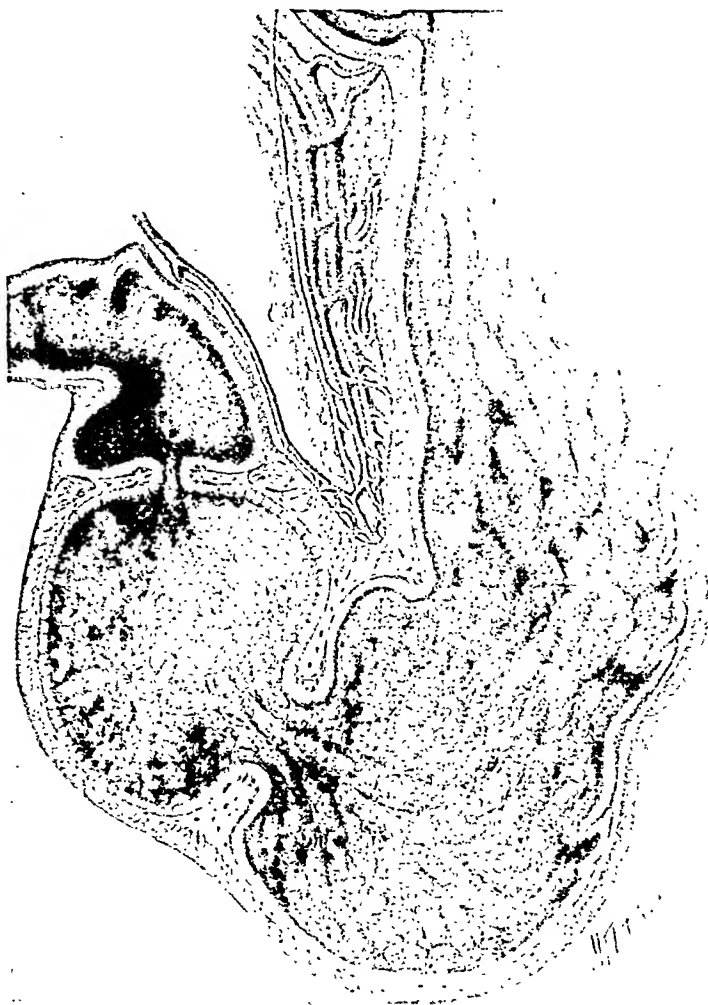


Fig. 2.—Inside of normal stomach with antrum moderately dilated, showing the corpus with its longitudinal and crinkled rugae, the antrum without rugae, cap, pyloric valve, and peristaltic contraction caused by the muscularis mucosae.

Microscopical Findings.—After a comparison of the gross pathologic findings (Fig. 3) with those of the normal rugae of the

Fig. 3.

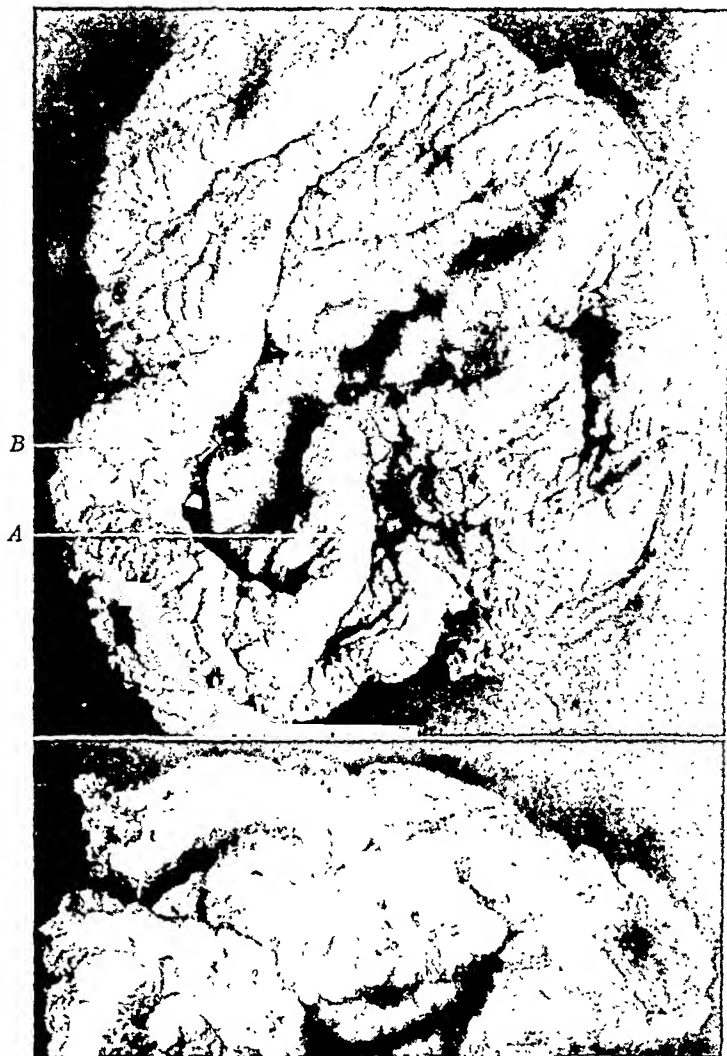


Fig. 4.

Fig. 3.—Untouched photograph of the uncut section of the inner surface of the pyloric end of the stomach. *A*, Immense rugae; *B*, crevices between the rugae.

Fig. 4.—Longitudinal section through the gross specimen.

mucosa, one might ask whether there is justification for the adoption of the term "hypertrophic gastritis." Does the mere enlargement of rugae justify one in classifying the condition as a pathologic entity? The answer would be in the negative were it not for strong substantiating microscopical evidence to the contrary.

An intensive study of a longitudinal section (Fig. 4) through the entire length of the gross specimen reveals that it includes a section of the gastric wall for a distance of about 2 inches proximal to the pyloric valve, through the valve, and includes about $\frac{1}{2}$ inch of the cap. This section includes the thick, fan-shaped pyloric muscle, two large mucosal folds in the stomach, the pyloric valve and a small segment of the cap beyond the termination of the muscularis mucosae and the submucosa. In this section, the rugae are cut transversely, but the pyloric valve is cut obliquely. A flap of redundant ruga projects beyond the proximal cut edge of the muscular coat. These two rugae and the mucomembranous fold which constitutes the pyloric valve correspond with the rugae and pyloric valve as observed roentgenologically, as we shall see later.

The findings are shown still better in a stained microscopical section (Fig. 5) which is so large as to include a longitudinal section through the entire length of the specimen. We are indebted to Miss Gregory, laboratory technician in the Department of Experimental Surgery, Columbia University, for the beautiful preparation of these large microscopical sections which are cut so thin that they serve for microscopical investigation as well as for microphotography. Miss Gregory's services have been extended through the courtesy of Dr. Stout.

Adjacent serial sections were stained with hematoxylin and eosin, the trichrome stain of Maussion, the Mallory stain, a stain for mucin, the so-called "Spanish stain," "Van Gieson's stain," and Laidlaw's silver stain for intracellular spaces. Each of these stains aided us in the study of this problem, but I believe that the trichrome stain of Maussion served us best.

The large microscopical section (Fig. 5) shows the pyloric end of the stomach, the thick fan-shaped muscle terminating at



Fig. 5.—Magnified photograph of microscopical section including entire length of specimen. *A*, Muscularis propria; *B*, submucosa; *C*, hypertrophied mucosa thrown into folds; *D*, fan-shaped muscle; *E*, pyloric valve; *F*, wall of cap; *G*, dilated blood vessels; *H*, dilated lymph channels, *I*, cyst.

the pyloric valve, the mucomembranous fold of the pyloric valve, cut obliquely, the thin-walled cap, or so-called "first portion of the duodenum," with the muscularis mucosae and submucosa absent in this region. There are two large rugae composed of mucosa, muscularis mucosae and a core of submucosa. In the ruga to the right, the fold is intact; in that to the left the mucosa was destroyed during preparation of the specimen, before the section was cut. This was no fault of Miss Gregory. This ruga therefore does not appear as large as it really was. The muscularis mucosae of one of these rugae contains an immensely dilated blood vessel and the submucosa in the other contains an immensely dilated lymph channel. The punched-out hole in the mucosa is a small cyst.

Magnified photographs of both the gross and microscopical sections (Figs. 6, 7) show the cardinal characteristics of the lesion, namely, an increased length and thickness of the mucosal coat which is thrown into hypertrophied folds or rugae. The question now arises: What tissues within these folds increase in size to cause the hypertrophied rugae? That is, how do the tissues that form these rugae differ from those that form normal rugae?

Each of the rugae contains a double fold of mucosa, one going into it and another coming out of it, as well as a core of submucosa. The muscularis mucosae, which is firmly fixed to the mucosa, also goes into each of the rugae and comes out again. The muscularis propria does not participate in the rugae.

Variations from normal are much less evident in the microscopical sections than in the gross specimen and still less evident than in a freshly removed surgical specimen. In both of these, the findings are less apparent than one would expect them to be from an observation of the roentgenological findings. We believe that this apparent diminution in the microscopical section is due to fixation of the specimen with formalin and to the subsequent dehydration by alcohol incident to preparation for microscopical section. All of the cells are somewhat diminished in size by fixation and the fluid of the edema is absorbed by the alcohol. Thus the specimen diminishes or shrinks in size so



Fig. 6.

Fig. 6.—Dilated convoluted tubules near the base of the submucosa.

Fig. 7.

Fig. 7.—Same region, larger magnification, showing granular cells and tendency to basement membrane.

that the only microscopical evidence of the edema consists in a few small areas of pale pink, homogeneous tissue in the reticulum of the mucosa just beneath the epithelium. This edema may also be detected deeper in the specimen, just beneath the submucosa. Blood vessels or lymph channels that, during life, have been distended or overdistended, are diminished or contracted, as the blood or lymph seeps out after operation. With a lower power magnification ($\times 50$) the structures of the walls of the dilated blood vessels and immensely dilated lymph channels in the submucosa are distinctly shown, findings that indicate the existence of engorgement during life (Figs. 8, 9). Many of the blood vessels are filled with corpuscles to a greater degree than usually seen in microscopical sections of normal gastric mucosa. The mucosa itself is thicker than normal. The individual tubules are longer and seem to be made up of an increased number of columnar and epithelial cells. The lumen of many of the tubules is distended, sometimes to macroscopical size, as shown by the punched-out area in the photograph of the microscopical section. The increased secretion in these blocked tubules to some extent is not unlike follicular cysts of the ovary. These cysts have been described by Windholz, Kalima, and other observers. They have a connective tissue basement membrane lined with layers of columnar cells.

The lumen of the stalk or shaft of the gastric tubule is dilated or overdistended and the cells surrounding the lumen are flattened or cuboidal, and are more granular than normal. The same process is observed in the convoluted portion of the tubular glands. Even in this early, slight stage of dilatation, a tendency to a basement membrane is observed. Although each of the individual tubules is increased to only twice its normal size, and while this is microscopical, the multitude of tubules so enlarged adds markedly to the bulk of each of the hypertrophied rugae.

The reticulum supporting the shafts of the tubular glands, particularly that portion which is near the surface of the mucosa, is infiltrated with round cells. This adds, also, to the thickness and length of the mucosa. The lymph follicles are not more numerous than normal. This finding is in contradistinction to



Fig. 8.

Fig. 8.—Large and small cysts of the mucosa lined with columnar epithelium on a basement membrane.

Fig. 9.

Fig. 9.—Edema and round-cell infiltration increasing size and thickness of mucosa.

the enlarged and broken follicles observed in atrophic gastritis and in ulcerative gastritis. The few lymph follicles that are observed have, also, the characteristic findings of hyperemia observed in other regions of the section. Thus, the hypertrophy or hyperplasia of the small round cells in the stroma, the hypertrophy of the tubular cells, the hypertrophy or dilatation of the lumen of the tubules, the dilatation of the blood vessels and lymph channels are all prime factors in a process of hypertrophy of the rugae of the mucosa and submucosa. Thus, the term "hypertrophic gastritis," although not new, seems accurately to designate this pathologic entity.

If one will revert now to Fig. 1, which shows the gross pathology, and recollect that each large mucosal fold is composed of the hypertrophied tissue just described, it becomes evident that the lesion is a pathologic entity from its earliest stage. If one concentrates on the findings shown in Fig. 1 and on the manner in which these large rugae encroach upon the lumen of the stomach, one begins to realize that they should cause unusual roentgenological findings when the barium mixture has worked its way into the crevices between the large rugae, and, indeed, they do. But before describing these pathologic findings in roentgenograms, one must know the appearance of normal rugae in various local regions of the stomach.

Roentgenological Appearance of Normal Rugae.—The definite differentiation between normal rugae and pathologic rugae is one of the most crucial points in this communication. I fear that clinicians, pathologists, surgeons, and even roentgenologists may mistake the roentgen findings of normal rugae for those pathologic rugae that are characteristic of hypertrophic gastritis. It would be a very serious matter to base the indications for surgical treatment on roentgenological findings caused by normal rugae, the appearance of which may be so easily exaggerated by some unusual technic, such as the employment of a small amount of barium mixture or the use of a thick paste smeared on by pressure, now coming into vogue. Therefore, it seems wise to describe and illustrate, in some detail, the roentgenological appearance of normal rugae, especially as exaggerated by inten-

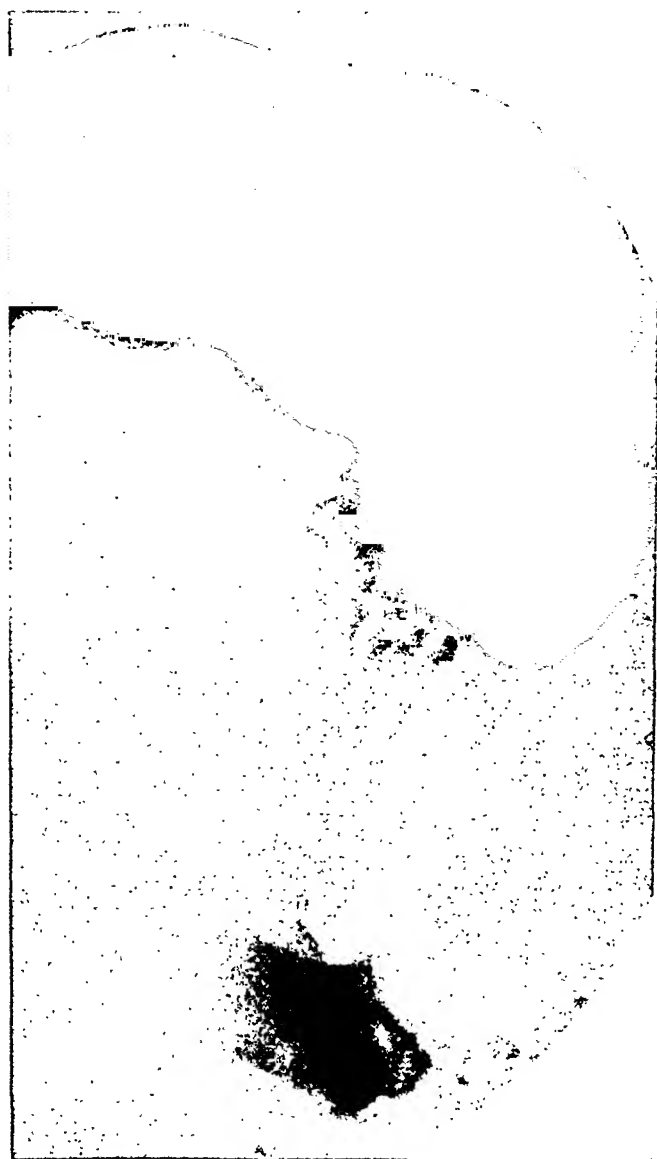


Fig. 10.—Actual size and distribution of normal rugae in the pyloric region shown for comparison with hypertrophic rugae in Fig. 12.

tional or unintentional pressure, or by the modern meal of only a small amount of barium (Figs. 10, 11).

The roentgenological findings characteristic of rugae have been recognized for two decades; in fact ever since the direct



Fig. 11.—Normal gastric mucosa shown by special sedimentation technic.

detection of morphological changes in the wall of the stomach became the criterion for the roentgenological diagnosis of gastric lesions. The mucosal pattern, or mucomembranous relief, was studied intensively as early as 1910. Recently, the roentgeno-

logical appearance of the rugae has become the central subject of reinvestigation, particularly abroad, being discussed variously as "mucomembranous relief," "mucosal pattern," "pressure technic," "sharp shooting," etc.

During the last two decades the rugae have been observed in such a large percentage of cases examined in our routine procedure that we have come to recognize a normal size, shape, and distribution of the rugae in the various regions of the stomach, referring to them as rugae of normal size and distribution. These rugae have distinctly different characteristics in the various regions of the stomach, especially in a region where the lumen is diminished in size either by muscular contraction or as the result of pressure from without.

Normal rugae in the pyloric region may appear, roentgenologically, as fine, parallel lines within the region of contraction of the strong, fan-shaped muscle of the pylorus, or, during relaxation of that muscle, they may be broader and thicker, although still running parallel with the long axis of the pyloric canal. The roentgenological prominence of these rugae is due to a diminution of this region by habitual pylorospasm, or by pressure from without, usually pressure by the spine or aorta. They are still within normal limits, however, so far as size is concerned. Some of the rugae, during the state of relaxation, may be so much larger than the fine parallel lines that are seen during contraction, that I am afraid they may be misinterpreted as rugae characteristic of hypertrophic gastritis.

Normal rugae along the greater curvature are generally much larger than the rugae in the pyloric region. This increase in size is due to the great increase and diminution of the length and diameter of the greater curvature during the extreme stages of distention and contraction of the stomach. Therefore, large rugae observed only in this region should be considered of little or no clinical significance, unless extremely large.

Roentgenological Findings of Hypertrophic Gastritis.—During the routine gastro-intestinal examination, administering about 8 ounces of barium and water mixture, the barium seeps in between the large pathologic folds and the roentgenological

appearance is as though the patient had swallowed a bunch of "night walkers" before drinking the opaque mixture. These large rugae so completely fill the lumen of the stomach in the

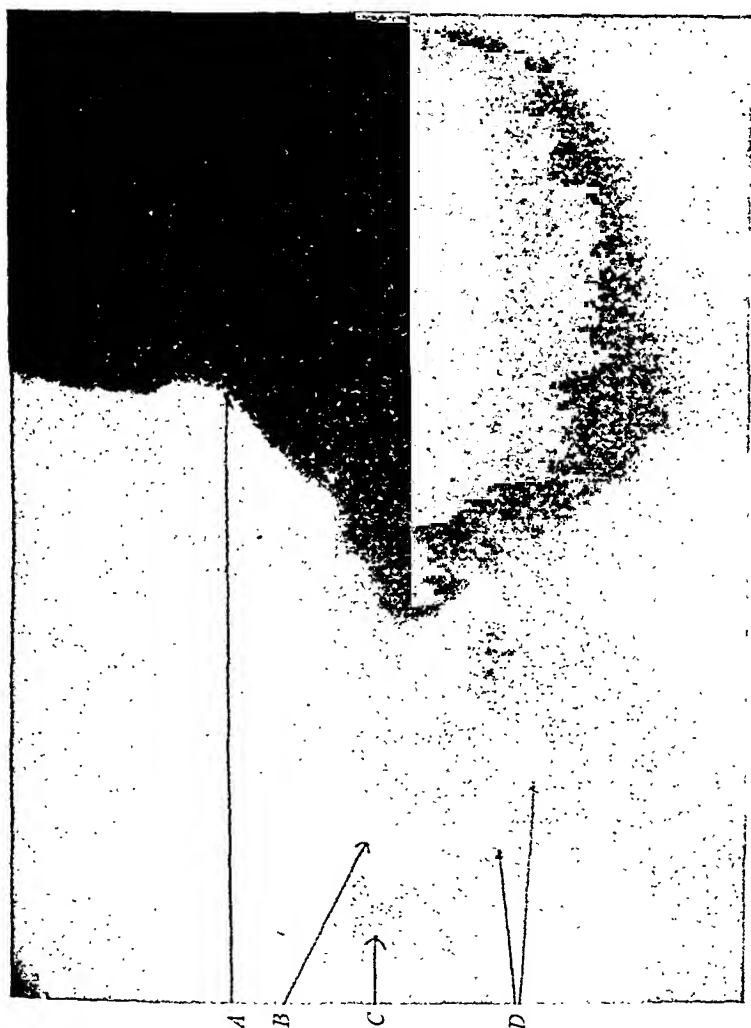


Fig. 12.—Hypertrophic gastritis: *A*, Normal stomach; *B*, hypertrophied pyloric valve; *C*, cap; *D*, hypertrophied mucosal folds.

pyloric region, in a case of hypertrophic gastritis, that only the interstices between the large rugae are filled with barium, providing very characteristic roentgenological findings (Fig. 12). In this region each of the rugae may be outlined, perhaps for the

Fig. 13.

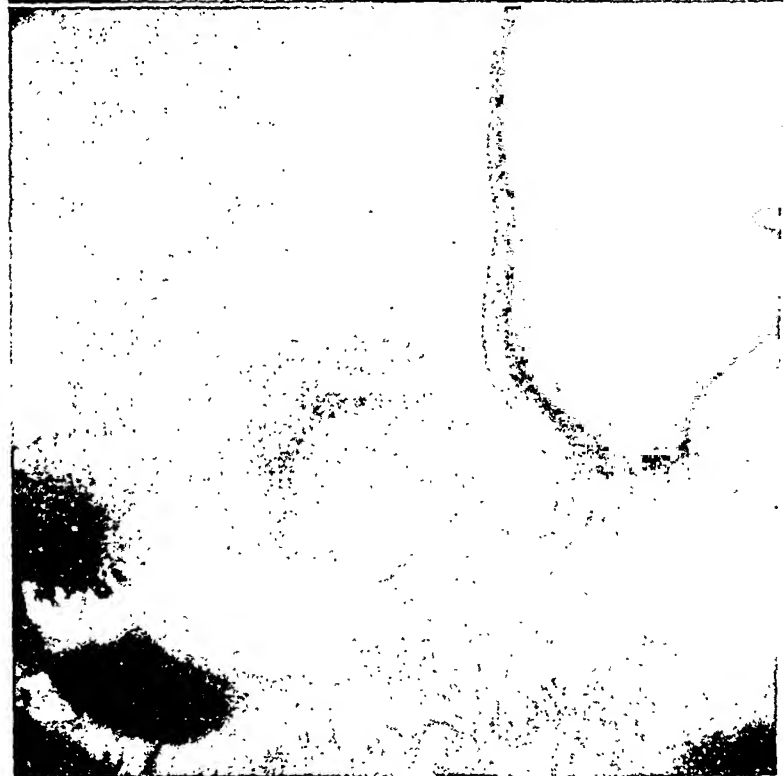


Fig. 14.

Fig. 13.—Case I. Hypertrophied mucosal folds crowded into pyloric canal resembling cancer.

Fig. 14.—Case I. Late stage before operation, showing extreme gastric spasm.

entire course of the ruga, by a small amount of barium seeping in between the folds. The morphological changes in the wall of the gut cause the roentgenological findings that are the criteria for the roentgenological diagnosis of hypertrophic gastritis. Even in the very early stage of this condition, when only a small region of the stomach is involved, the author believes these rugae to be individually pathologically enlarged. In other words, hypertrophic gastritis is not a mere exaggeration in size of normal rugae, such as is often observed in a routine roentgenological examination, particularly when there is pressure from without or some degree of pylorospasm caused by a contraction of the fan-shaped muscle, but is actually a pathologic hypertrophy of the rugae.

Hypertrophic gastritis may involve the entire stomach yet apparently be limited to rugae in the pyloric region. I say "apparently" because overdistention of the corpus may obscure the rugae in this region. Because large rugae occur normally along the greater curvature, they are frequently misinterpreted as the finger prints of cancer. More often, large rugae in the pyloric region make one immediately suspicious of cancer, whereas, in reality, the large rugae are due to hypertrophic gastritis and not to carcinoma. Indeed, in our first case, where the progressive course of the lesion was observed over a considerable period of time, the author was suspicious of cancer in spite of the fact that the irregularities were not as constant as one expects to find in cancer (Figs. 13, 14). When the hypertrophic rugae involve the entire anterior or posterior surface of the corpus they are of clinical significance (Fig. 15). The roentgenological findings are generally most distinctly observed when the roentgenograms are made with the patient in the prone posture. In the erect posture, the weight of the barium mixture may obliterate all rugae except at the pyloric canal just proximal to the valve, causing a finding that very closely simulates pyloric cancer (Fig. 16).

Thus far, we have observed the characteristic gross pathologic appearance of the rugae in hypertrophic gastritis and have compared these with the appearance of the inside of the normal

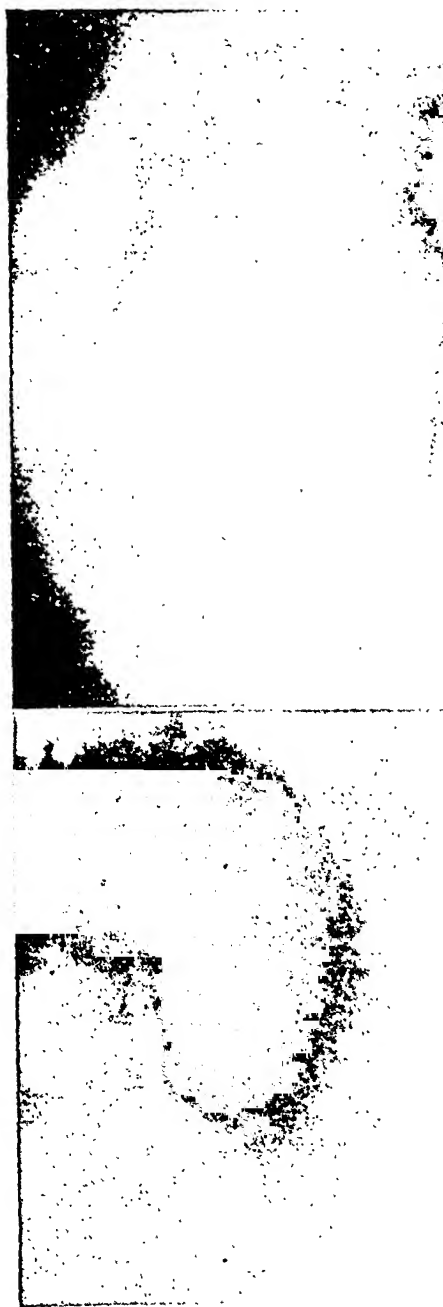


Fig. 15.—Case II. Roentgenographed at the Beelman Street Hospital by Dr. Ramsay Spillman and presented herein through his courtesy.

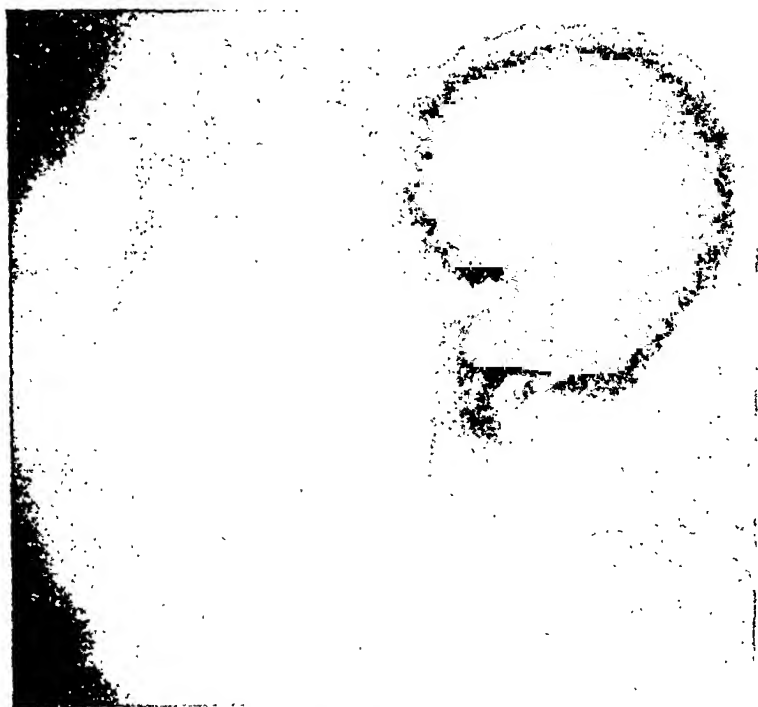


Fig. 16.—Roentgenogram made in the erect posture, suggests the possibility of malignancy.

stomach. We have observed, also, the microscopical structures within the pathologically enlarged rugae, have correlated the gross and microscopical findings with the roentgenological findings of hypertrophic gastritis, and have differentiated the roentgenological findings of normal rugae, as shown more distinctly than usual either by intentional or by unintentional pressure, from the roentgenological findings of hypertrophic gastritis. Let us now consider the rôle of this lesion in pyloric stenosis, gastric retention, gastric spasm, retention of food as an irritant, and consider its symptomatology in general.

Pyloric Stenosis.—True organic stenosis is not observed in this disease. Even when the pyloric canal is practically filled with hypertrophied rugae, as shown in Fig. 14, there is little or no delay in the passing of the first swallow of barium mixture through this region into the cap and duodenum. This lack of delay is confirmed by Spillman's fluoroscopical report, in Case II, where he states that he saw the mixture pass unusually rapidly through the stomach into the duodenum. This rapid progress, or lack of delay, rather than gastric retention, is the true measure of pyloric patency.

Gastric Retention.—This is very different from pyloric stenosis. Barium or food may be retained in the stomach much longer than normally, despite the fact that the first swallow of barium passes through the pylorus more rapidly than normal. This lack of evacuation is due to two factors: first, stomachs with hypertrophied rugae do not have the power to evacuate themselves completely in a normal period of time so that the barium or food becomes incarcerated in the deep fissures, or sulci, between the mucosal folds, or rugae, and remain there for a long time after the bulk of food has been evacuated from the stomach; secondly, gastric retention may be due to spasm of the fan-shaped muscle an hour and a half or two hours after eating. We believe the first factor in gastric retention, that is, delay in evacuation, to be due to ineffectual gastric peristalsis. Gastric peristalsis is the function of the muscularis mucosae and this muscle is involved in each of the hypertrophied rugae. With regard to spasm as a factor in retention, in the later stages

of the case that we followed most intensively there was evidence of extreme spasm of the entire stomach in many of the roentgenograms. Whether this spasm was a purely functional derangement or an attempt to evacuate the stomach, we are unable to state.

Retained Food as a Gastric Irritant.—The fact that the stomach is not able to evacuate completely its content lodged between rugae, and the fact that fragments of food so retained continue to stimulate gastric secretion, are important clinically in the production of highly acid secretions. These factors, in combination with the strong contraction of the fan-shaped muscle, would readily account for the pain or distress occurring one or two hours after eating and continuing until gastric secretion is neutralized or more food is eaten. Additional food, particularly solid food, tends to separate the mucosal folds and gives the strong fan-shaped muscle something on which to contract or to macerate other than the hypertrophied rugae. The lancinating pains, often radiating to the back, are probably associated with or caused by marked general gastric spasm (Figs. 12, 13). Closure of the pyloric canal by a strong, prolonged contraction of the fan-shaped muscle may exist during the major portion of each gastric cycle; that is, if ten roentgenograms were made during a period of twenty seconds, more than five would show the pyloric canal closed; if only two or three were made, all might show it closed. Roentgenograms showing a firm closure of the pyloric canal very closely resemble those of pyloric cancer. Indeed, serial roentgenography is often necessary to make the differential diagnosis between these conditions.

Redundant folds of mucosa may be forced through the pyloric valve by the strong contraction of the fan-shaped muscle, and cause a condition similar to hemorrhoids. This is not precisely the lesion we are considering, however. In those cases the mucosa need not be thrown into folds that are larger than normal, although the symptoms may be very similar to those of hypertrophic gastritis. This condition is mentioned for the purpose of its differentiation.

Multiple Polypi.—These cause roentgen findings similar to

those of hypertrophic gastritis, except that, in polyposis, the mucosa protrudes into the lumen of the stomach in spherical rather than in cylindrical masses. They remind one of currants or small grapes rather than "night walkers." Both conditions may be shown distinctly when the stomach is partly filled, with the patient prone, and be largely or completely obscured by overdistention, sometimes by moderate distention of the stomach with the opaque medium.

The gastric mucosa may become so greatly hypertrophied that it almost completely fills the lumen of the stomach. In such cases, the barium mixture seeps through the folds of mucosa and gives the impression of a sponge saturated with barium mixture (Fig. 17). Profuse hemorrhage was the cardinal symptom in one such case, Case III. At the time I first saw this case I did not associate it with the group of cases that we have assembled for study under the term "hypertrophic gastritis." It was not until we had observed an intermediate case that reminded Dr. Pound, my associate, of this earlier case, that we realized that Case III represented an advanced stage of hypertrophic gastritis (Fig. 18).

Symptomatology.—In general, the symptoms of hypertrophied gastric mucosa are similar to those of ulcers of the pyloric canal, that is, the so-called "prepyloric ulcers" that occur just proximal to the pyloric valve, within the region of the stomach that is surrounded by the strong fan-shaped muscle. The symptoms are similar, also, to those of pylorospasm of this region due to contraction of the fan-shaped muscle, without an ulcer.

The cardinal symptom is a periodic attack of pain or distress in the epigastrium or in the right hypochondrium, occurring one and a half or two hours after eating and persisting until relieved by alkali or food. The relief thus furnished is not as prompt or complete as in cases of postpyloric ulcer. The symptoms recur at frequent or infrequent intervals over a long period of time. In one case, the history dated back ten or twelve years. At first the symptoms were not severe and were infrequent, increasing gradually. This is at variance with the sudden, severe

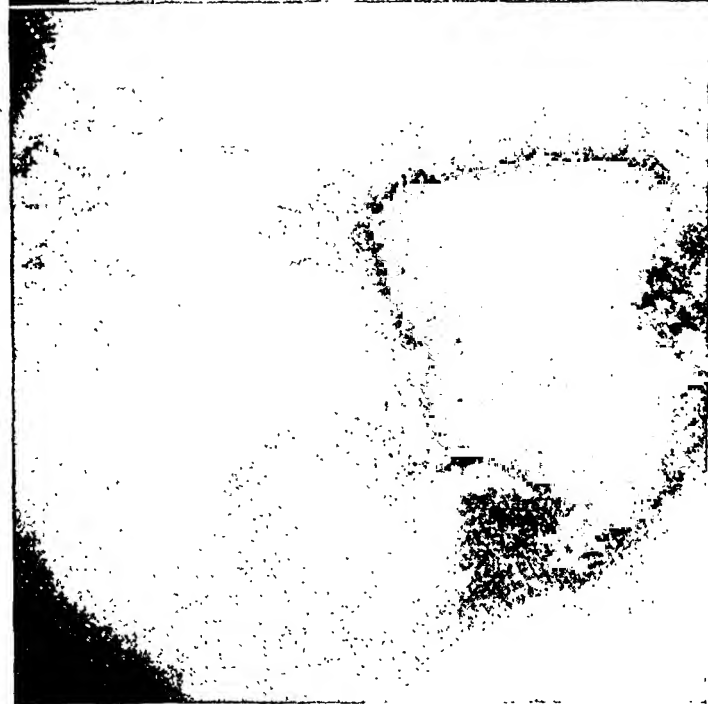


Fig. 17.

Fig. 17.—Markedly hypertrophied mucosa with profuse hemorrhage improved by roentgen therapy. (Case III.)

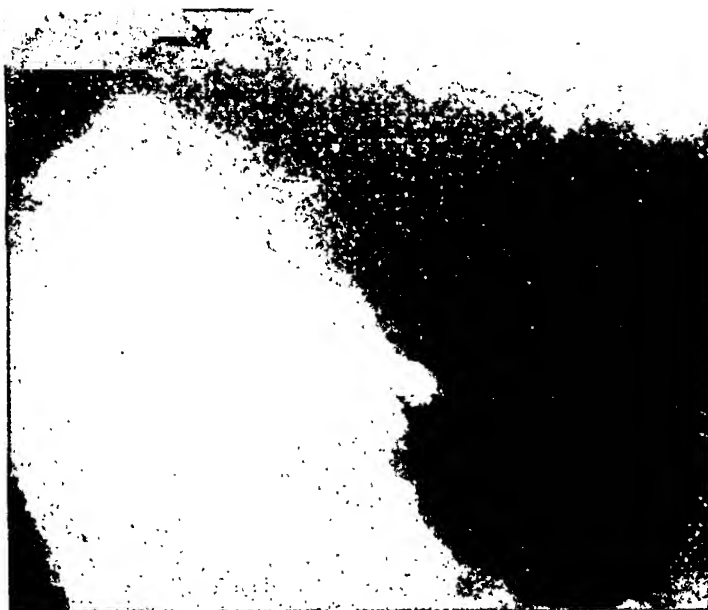


Fig. 18.

Fig. 18.—Markedly hypertrophied mucosa of corpus or body of stomach. Pyloric antrum normal. (Case IV.)

onset of the initial symptoms of postpyloric ulcer. The attacks of pain gradually increase in frequency and severity until, in later stages, they are described as lancinating, and may run through or be referred to the back.

"Bloating" or "gas pains" seem to be favorite terms for the patient to use in describing his symptoms. In the cases that we have observed, however, the roentgen examination has not revealed an excessive amount of gas in the stomach. We have very grave doubts as to whether the patient's "gas pains" or "bloating" are in reality due to an overdistention of the stomach with gas. These symptoms are much more likely caused by pylorospasm. The patient, in an effort to expel gas not originally present, sucks in air through the esophagus and it is this air that he belches up, calling it "gas."

Nausea and vomiting are not prominent symptoms during the early stage, but may occur in the advanced stage. Vomiting, without nausea, or forced vomiting to relieve the symptoms, occur more often than does nausea without vomiting.

Physical Examination.—Palpation reveals tenderness in the epigastrium and perhaps a slight rigidity; no mass like an acute abdominal tumor mass is palpable.

Gastric analysis shows high acidity, the acidity increasing gradually with the severity of the symptoms and the advancement of the lesion, as observed roentgenologically. Blood may or may not be present in the gastric contents removed by tube. When present it may be of traumatic origin.

Examination of the Stool.—From our pathologic study of these cases, we believe small amounts of blood should appear in the stool, although the clinical histories available do not always record such an observation.

Progress.—We have not followed a sufficient number of these cases for a long enough time to know their progress. Apparently, there are periodic attacks with intervals of partial or complete relief of symptoms. In the cases that we have followed most closely, by means of clinical and roentgenological examinations, the progress of the lesion and the symptoms is much more rapid in the advanced stage of the lesion than in the early stage. As

a rule, the stage of rather rapid progress has been preceded by a long clinical history of repeated attacks.

Treatment.—Alleviation of the acute exacerbations with alkalies and antispasmodics and diet offer the best results. Jackson, of Scranton, has recommended an excessively dry diet for a group of cases where the rugae are shown distinctly but not hypertrophied. This dry diet might be applicable to cases of chronic hypertrophy of the mucosa, but such normal rugae must be differentiated from the lesion of hypertrophic gastritis which is the subject of this communication. Articles of food known to cause the attacks of pain and distress should be eliminated. Considering a possible allergic etiology for this condition, thorough tests to eliminate certain harmful articles of food may be effective in preventing recurrent attacks.

In Case III, which is illustrated in Fig. 18, hemorrhage was one of the principal symptoms of which the patient complained. She was under observation for a considerable period of time and various medications were of little avail. Deep therapy was then suggested and five exposures of thirty minutes each, 185,000 volts, 4 Ma., 50 cm. distant, $\frac{1}{2}$ mm. of copper and 1 mm. of aluminum, were given on the days recorded in the case report. Even the first treatment had a very marked effect on the hemorrhage. Improvement ensued rapidly with improvement also of all the other clinical symptoms. Although this marked improvement has continued, an x-ray examination made immediately after the treatment, and another six months later showed very little change in the pathologic lesion. A very recent report by the attending physician indicates that the clinical improvement still holds.

In some cases, the symptoms may be so severe or so constant as to demand surgical treatment. Gastro-enterostomy is contraindicated, even where there is some stenosis and gastric retention, because the region of the stomach between the stoma and the pyloric valve will not "clear itself" after the bulk of food has passed through the stoma. Gastric resection or transection is indicated; resection, though the more severe procedure, provides an ample specimen to determine the character of the

lesion. Transection of the stomach, that is, the Devine operation, preferably as modified by Bancroft, is less serious but does not provide a satisfactory specimen for pathologic investigation. A partial gastrectomy was performed by Dr. William H. Bishop at the Fifth Avenue Hospital in the case that we have been able to study most intensively. We present below the complete clinical, roentgenological, surgical, and follow-up findings:

Case I.—W. R. H., white, male, age thirty-six years. Admitted November 30, 1927.

Chief Complaint.—Indigestion for one year; severe knifelike pains in right upper quadrant, coming on one and a half hours after meals, often radiating to the back.

Present Illness.—Patient has been troubled with belching of gas after meals for the past eight to twelve years. About one year ago he began to have attacks of abdominal pain, about one and a half hours after meals. He consulted a doctor who treated him for pus in the kidney, with some relief. A month or two later the patient was treated for indigestion and powders gave some relief. However, he continued to suffer off and on, the attacks of pain increasing in severity and frequency. Since June, 1927, he has had three attacks of pain a day, one after each meal, the pain being severe and knifelike in the right upper quadrant, sometimes radiating around to the back. He has had no nausea or vomiting. The pain is relieved by food and sodium bicarbonate. The symptoms follow the "pain, food, relief" cycle with clocklike regularity. There is a tendency to constipation.

Physical Examination.—Blood pressure, 90/64. Best weight, 163; average, 137; present, 131. Abdomen: No masses, tenderness or rigidity. Essentially negative.

Laboratory.—11/30/27: Gastric contents free HCl +50; total, 62.

12/2/27: Gastric contents, free HCl +32; total 85.

12/3/27: Gastric contents, free HCl +31; total 92.

Occult blood, negative.

11/30/27: Blood Wassermann, negative.

11/30/27: Hemoglobin, 100; red blood cells, 4,300,000; white blood cells, 5500; polymorphonuclears, 60; lymphocytes, 40.

11/30/27: Blood chemistry: Urea N, 14; uric acid, 2.3; sugar, 85.

12/6/27: Urine: Albumin, trace; hyaline casts, occasional.

Roentgenological Findings, October 25, 1927.—A series of films made of the stomach and intestines immediately, two, six, and twenty-four hours after the ingestion of a barium meal, show a very marked and persistent spasm involving the pyloric end of the stomach for a distance of at least 3 inches proximal to the sphincter and including the sphincter.

The rugae are hypertrophied and thrown up into large folds. There is no definite crater of an ulcer that can be identified. The cap is well filled and shows no constant deformity, and the stomach begins to empty itself in a normal manner. At two hours the stomach is half empty and the head of

the column has reached the rectum. The colon is well filled but the small intestine is empty. The appendix is filled.

At six hours the stomach is empty except for a few flecks of barium between the rugae at the pyloric end of the stomach. The colon is well outlined and only a small amount of barium remains in the small intestine.

At twenty-four hours the meal is scattered throughout the colon. The appendix is filled, angulated, and segmented.

Films of the colon show no evidence of cancer or obstructive loops or kinks in the colon or sigmoid. There is an indentation in the base of the cecum at the appendix attachment and the appendix is partially filled and at this time contains fecaliths. Films of the gallbladder region show no direct evidence of dilated or pathologic gallbladder and no stones.

Diagnosis.—From a study of these films I believe one is justified in making a positive diagnosis of extreme persistent spasm involving the pyloric end of the stomach. This has been present for some time and we are unable to detect any definite crater of an ulcer, although the possibility of a small crater could not be ruled out due to deformity resulting from the spasm. It has been our experience that cases with this type of lesion respond to no type of treatment with any degree of consistency. We believe this type of case is much more likely to develop malignancy in later years than any case of gastric ulcer. There is no obstruction to the passage of the meal through the intestinal tract and the passage of the meal was at a normal rate except for the delay shown in the two-hour film when the small intestine was free and the barium remained in the stomach and the colon was well filled with barium. There is no evidence of postpyloric ulcer. No obstruction. One is justified in making a negative diagnosis of cancer or obstructive loops or kinks in the colon and sigmoid. There is evidence of chronic involvement of the appendix and this may be associated with the spasm involving the pyloric end of the stomach. There is no direct evidence of gallstones or dilated or pathologic gallbladder.

November 23, 1927.—Films of the stomach show that the lesion involving the pyloric end of the stomach instead of improving is definitely worse than it was a month ago. There is more irritation and more spasm than was shown in the previous films. We are still unable to make out a definite crater formation of an ulcer and believe that this is an infiltrative lesion involving all the pyloric end. The stomach was fluoroscoped after four hours and was entirely empty showing that there was no obstruction.

February 9, 1928.—Films of the stomach made immediately and four hours after a barium meal show that the pyloric end is apparently functioning normally after resection. The duodenum has straightened out and there is a tendency toward the formation of a cap. At four hours most of the meal has been evacuated from the stomach. There is no obstruction and there is no increased spasm. I believe that the x-ray findings indicate a very exceptional surgical result at the present time.

Preoperative Diagnosis.—Carcinoma of the pylorus.

Purpose of Operation.—Exploratory laparotomy.

Operation Performed.—Billroth I, Horseley modification. 12/7/27:
Findings: A large, left median abdominal incision was made. Stomach and

duodenum were of normal size. The stomach walls seemed thick and injected. The first portion of the duodenum was easily mobilized and a pylorotomy was performed, removing about 3 inches of the stomach and 1 inch of the duodenum. Billroth I with Horseley's modification completed. No drainage. Usual skin closure of catgut in the peritoneum, chromic for fascia, and silk for the skin. Appendix not inspected. Gallbladder normal. Time: 2.20 to 4.05.

Pathologist's Report.—Congestion of wall of viscus.

Final Diagnosis.—Congestion of wall of viscus.

Discussion.—The pyloric resection consisted of such a short area of the stomach that it could not be prepared by paraffin in our usual manner. A magnified photograph of the gross specimen shows its similarity to a bunch of "night walkers" and corresponds absolutely with the roentgen findings (Figs. 13, 14). The rugae were two or three times as large as normal, even after they had been fixed with formalin and their depth is shown in photographs of the cut section (Figs. 3, 4).

The preoperative diagnosis of cancer was based on the clinical progress of the disease and the fact that we were not willing to make a negative diagnosis of cancer on the basis of the x-ray findings. The pathologist's report was negative for cancer and mentioned the congestion of the wall of the viscus. Subsequently, we undertook an intensive pathologic study of the gross and microscopical sections, furnishing the basis of the observations that we have set forth above concerning hypertrophic gastritis.

Case II.—Patient L., male, taxi driver, twenty-three years old; admitted to Beekman Street Hospital, observed by Dr. Ramsay Spillman. Admitted to Dr. R. H. Kennedy's service, September 26, 1930. Discharged, October 11, 1930.

Chief Complaints.—Pain in abdomen and vomiting.

Past History.—Pleurisy in left lower chest six years ago. Gonococcus infection four years ago and again two months ago; syphilis denied by name and symptoms. Was admitted to New York Hospital, September 2, 1928, Dr. Gibson's service, with a diagnosis of chronic appendicitis. Appendectomy was followed by uneventful recovery and patient was discharged September 15, 1928. While at the hospital, the Graham test was negative and the surgical notes stated that operation revealed no pathology of the gallbladder. Following the removal of the appendix, patient was entirely well until four months ago when, for three days, his bowels did not move and he was "bloating up," obtaining relief finally by catharsis.

Present Illness.—Two weeks ago the patient began to have very slight,

but steady pain in the lower abdomen, the patient pointing to the region of its location as midway between the navel and the symphysis. At its onset, the pain lasted three days. It did not radiate. There was no nausea or vomiting, but the patient was constipated. The pain disappeared for several days and returned a week ago. The day before admission, he vomited four times, and once after admission: the vomitus was greenish in color. No chills. Pain has increased since yesterday. For past year and a half has had considerable belching and feels bloated after eating. For past four months has had some heart burn. For past twelve or thirteen weeks has been unable to get work. Denies anything unusual in his diet that could throw light on his illness other than, possibly, a little "home brew" shortly before onset.

Physical Examination.—There is definite marked tenderness in the epigastrium, extending to about 2 inches to the right of the midline. Moderate, but definite muscular spasm in this area. Liver and spleen not felt.

Impression of intern: Cholecystitis? Intermittent chronic intestinal obstruction from adhesions? Gastro-enteritis?

Temperature.—On admission the temperature ranged from 101 to 101.5 F. for four days, then not over 99 F. for five days; on the fourteenth day it went up to 101.3 F. and the next day dropped to normal, remaining normal until his discharge, October 11, 1930.

Laboratory.—*Gastric contents* before test meal, October 8, 1930: 5 cc., total acidity, 67; free HCl, 40; lactic, 0; trace of blood. After test meal, 6 cc. recovered; total acidity, 25; free HCl, 15; lactic acid, 0; blood, heavy trace. The swallowing of the tube caused considerable retching and made the patient feel much worse than he had felt for several days, during which he had been feeling quite well.

Blood Counts.—Not remarkable.

Roentgen Notes by Dr. Spillman.—"On fluoroscopying the stomach, September 29th, I was struck by the sudden passage of barium through the pylorus, in amounts sufficient to dilate the upper jejunum. The other striking feature was the prominence of the rugae. I expected from the sudden rush of barium that the stomach would be empty long before three hours, but a film at three hours showed a residue of perhaps one third of the meal. At six hours there was no retention.

"The precipitous departure of barium at first made me concerned over the possibility of infiltration of the pylorus by a carcinoma, but the films did not bear this out. The cap filled very poorly and barium did not remain long in it. This suggested an ulcer or duodenitis.

"On October 10th I fluoroscoped the stomach again and made more films. The rapid emptying was no longer a feature, but I could not fill the antrum normally by an manipulation, and films showed that the mucous membrane appeared to be encroaching on the lumen to a considerable degree. The defect did not match up with films made September 29th, which I felt ruled out malignancy. I suggested the possibility of polyposis, but stated that this stomach was unique in my experience, and that any diagnosis would be speculative. A spinous projection from the top of the cap on the upper left side suggested a duodenal ulcer, but at Dr. Cole's conference, when the stomach was diagnosed as having a serous infiltration of the mucosa, this

projection was regarded as an incomplete filling of the cap. (Possible line of barium in a fold or mucosa?)"

As the patient felt well and there was not sufficient surgical evidence to justify laparotomy, he was discharged, to report to the surgical out-patient department in two weeks.

Discussion.—This is an excellent description of the confusing roentgen findings caused by chronic hypertrophy of the gastric mucosa. The findings were not caused by the distinct showing of normal rugae; they were not characteristic of cancer because they were not constant in the several films of one examination or at different examinations; and they were not the findings of an ulcer because there was no crater; and they were not the round markings of multiple polypi.

Case III.—Mrs. R., twenty-six years, white, American housewife. Admitted to Fifth Avenue Hospital November 15, 1929, discharged January 23, 1930.

Present Illness.—Has been vomiting since childhood. Nausea induced by riding in an automobile or car would cause her to vomit, but not regularly, only once a month or so. This kept up until March, 1929, when she suddenly began to vomit after every meal. At times, on finishing eating, the food would come back into her mouth and she would spit it out. It never came up forcibly. She never vomited any coffee ground food or any blood. The stools were never clay colored, bloody or tarry. She never had any pain in the stomach. She consulted a physician and was helped by medical treatment. After vomiting a meal, she could often go back and eat again, keeping this down. The vomiting episodes came down to once a day but have kept up to last week. She has lost about 20 pounds in weight. There have been no quarrels, no known psychic cause of this vomiting. She has noticed edema of her ankles for past eight years and has known that she was anemic for the past seven months. She does not have nosebleeds or profuse menstruation. Has never been jaundiced. Has no tingling or numbness of fingers. She does get short of breath on climbing stairs.

The patient has been on a liver diet for the past six or seven months, eating from $\frac{1}{4}$ to $\frac{3}{4}$ pound of liver a day. She has had a varied diet, eating vegetables, fruits, meats, and milk and eggs. She has a fair appetite. Her weight varies normally from 135 to 165.

Past History.—Negative.

Family History.—Negative.

Physical Examination.—Marked anemia of mucous membranes. Heart normal. Glands, no enlargement. Thyroid, palpable but not enlarged. Thorax, normal. Lungs, negative. Heart, normal in size and shape; soft, systolic murmur at apex; blood pressure, 105/65. Abdomen, soft; no masses or tendernesses. Liver and spleen, not palpable.

Laboratory.—11/6/29: Wassermann examination, negative.

Urine Examination.—Acid reaction; specific gravity, 1010; faint trace of albumin; no casts; no sugar; few white blood cells.

Hematologic Examination.—Hemoglobin, 35 per cent; red blood cells, 3,200,000; white blood cells, 8400; polynuclears, 65; lymphocytes, 35; reticulated cells, 1 per cent. Platelets, 280,000. Coagulating time, four minutes, bleeding time, three and a half minutes.

Blood Chemistry.—Urea N, 15; sugar, 100; creatinin, 0.9; Van den Berghs, both negative; Fauchet, negative, icteric index, 6.8.

11/7/29: *Fragility Test.*—Hemolysis begins at 0.475, ends at 0.350.

Gastric Contents.—Fasting: 25 cc., opaque, straw colored; odor, negative; mucus, stringy; sedimentation, negative; bile, negative; blood, 2 plus; free HCl, negative; total, 14; lactic, 0.

Two Hours.—Twenty cc.; opaque, straw colored; odor, negative; mucus, stringy; sedimentation, negative; bile, negative; blood, 1 plus; free HCl, negative; total, 20; lactic, 0.

11/9/29: *Phenolsulphonphthalein*: First 54; second, 10; total, 64 per cent.

11/9/29: Stool: No ova or parasites found. Blood, positive.

11/15/29: Stool: Blood, positive.

12/2/29: Hematology: Hemoglobin, 45 per cent; red blood cells, 3,700,000.

12/5/29: Stool: Occult blood positive.

12/6/29: Stool: Occult blood positive.

12/7/29: Stool: Occult blood strongly positive.

12/10/29: Hematology: Hemoglobin, 50 per cent; red blood cells, 3,800,000.

12/16/29: Stool: Occult blood strongly positive.

1/3/30: Stool: Occult blood positive.

12/18/29: Hematology: Hemoglobin, 58 per cent; red blood cells, 3,900,000.

12/26/29: Hematology: Hemoglobin, 70 per cent; red blood cells, 4,300,000; white blood cells, 5080; polynuclears, 54; lymphocytes, 43.

12/27/29: Hematology: Hemoglobin, 72 per cent.

Roentgen Reports.—11/11/29: A gastro-intestinal examination revealed a rather extensive process involving the lesser curvature surface of the stomach. We are unable to state the etiologic factor and a differential diagnosis lies between an extensive ca. and extensive infiltration from ulcerations. The series will be rechecked.

11/15/29: Films of the lower end of the femur and upper end of the tibia show no pathologic change in the bones. Two separate examinations were made of the stomach after the administration of a barium meal and show an extensive infiltrative lesion involving the lesser curvature surface of the stomach from the sulcus to the esophageal opening. This deformity is constant. The wall is indurated and there are several irregularities. We believe that the evidence is in favor of a malignant process. Its location is such that it could not be removed surgically, and to rule out the possibility of a non malignant lesion, we believe that the stomach should be re-x-rayed after an

interval of a month or six weeks. There is slight gastric retention at six hours, but no evidence of pyloric stenosis or obstruction.

1/3/30: Films of the stomach show a marked change in appearance over previous films. There has been a progression of the lesion throughout the entire stomach. The contour of the gastric wall has altered markedly since the previous films and the appearance now is that of an extensive polypoid type of growth or cauliflower type involving the entire stomach. We are unable to state the etiology and have never seen a case of exactly this type, particularly when the change is so great within six weeks. We should like to make an additional examination on January 7th with the following preparation: a thorough catharsis between now and Sunday night; Tuesday morning a gastric lavage, with particular care that the stomach is entirely free from any type of food particles or fluid following the lavage, and at the time that we administer the barium meal.

1/14/30: Films of the stomach immediately and six hours after a barium meal show that the appearance of the stomach at this time is very similar to the original and to the second examination. The amount of deformity and the prominence of the rugae is not as marked as in the previous films, and I believe that at the previous examination some of the deformity was probably due to food in the stomach. The deformity shown at this time involves chiefly the cardiac end of the stomach, and we are unable to determine the etiologic factor. There is no obstruction, and the stomach is empty at six hours.

Progress Notes.—11/5/29: Patient admitted with some type of anemia to be worked out. Otherwise in excellent condition. Blood smears show only a marked secondary anemia. No normoblasts. No unusual white cells or unusual red cells. Platelets about normal in number, size, and shape. No parasites seen.

11/13/29: So far only a secondary anemia has been found, cause not established. No bleeding points found. x-Ray shows some curious stomach picture.

11/18/29: It is definitely settled that she has an extensive infiltration into the stomach—probably malignant. Patient's weight was 160, now is 128. Is perfectly comfortable with no gastro-intestinal complaints. Aspiration of gastric contents shows free blood, much mucus, with no lactic acid. Stools have occult blood.

11/29/29: 3.30 P. M. Armstrong oxycatalase 10 cc. injection intravenously. Technic good. Had slight pain in arm during injection and three or four hours later the elbow felt somewhat stiff. At 10 A. M. next morning still had slight stiffness of arm, but better than the evening before. During the night she had slight nausea but no vomiting. No vomiting next morning.

12/19/26: In good condition; up and about most of the time; eats well; vomits occasionally; stools are always positive for occult blood; is being fed Bland's mass and hemoglobin has risen from 35 to 50 per cent. Has lost no weight and is just as strong as ever, not very weak.

12/21/29: 4 P. M. Oxycatalase 10 cc. given intravenously in left arm. Technic good.

1/3/30: Patient's stomach was washed out with quart of warm tap water. The fluid returned a brownish white color; at one time it was colored slightly pink. Patient said the lavage relieved her of abdominal pain.

1/6/30: Temperature normal; condition the same; complains of some nausea; is getting dilute hydrochloric acid before meals.

1/13/30: Ten cc. of oxycatalase given intravenously in right arm. Slight nausea immediately on injection with burning at site of injection. Technic good. None in tissues.

1/23/30: Patient discharged, symptomatically improved. Actually the stomach process shows advancement. Diagnosis: Multiple polyposis of unknown character. Inoperable. Anemia much improved. Patient to continue treatment at home.

4/24/30: *Roentgen Examination*.—Films of the gastro-intestinal tract made immediately and six hours after a barium meal show that the enlarged rugae on the greater curvature surface are as prominent as in the previous films. There has been a change in the pliability of the lesser curvature and posterior surface from the cardiac orifice down almost to the pylorus. There is an area on the posterior surface near the lesser curvature in the cardiac region which appears to be an ulceration and has occurred since the previous examination. From this point downward the gastric wall shows a marked decrease in pliability. At the lower margin of this area near the pylorus it is thrown up into numerous folds, one of which suggests an ulceration. There is a small amount of gastric retention at six hours, which I believe is functional rather than organic in origin. Marked hypertrophy of the rugae is shown. We believe this to be an unusual type of process involving the stomach and believe the weight of the evidence is in favor of a malignant process.

Second admission to Fifth Avenue Hospital, September 16, 1930. Discharged November 11, 1930.

Present Illness.—Since last admission in November, patient has been very comfortable up until one month ago when she began vomiting, which was accompanied by pain in the epigastrium. Pain very severe and localized to a point in the epigastrium. Vomitus contains immediate food, no residual diet. No hematemesis. Bowels regular. No blood in stool. No coffee ground stools. Vomiting may or may not follow meals. No pain unless patient vomits. Considerable belching of gas. No pyrosis. No sour eructations.

Physical Examination.—September 16, 1930: Noticeable fulness in epigastrium. Localized tenderness at this point and sensation of a mass. Rest of abdomen negative.

Roentgen Examinations.—September 16, 1930: Films of the stomach immediately and six hours after barium meal show that the irregularities involving the rugae are greater now than in the previous films. The rugae show marked hypertrophy and irregularity and we are unable to state the etiologic factor. The cap is normal, and there is no obstruction.

October 15, 1930: Film of the chest shows no evidence of pulmonary tuberculosis involving the parenchyma of the lungs. No evidence of a lesion

of the lungs or pleura. The dimensions of the heart are within normal limits. There is a slight bulge in the region of the auricle. The aorta is normal.

November 11, 1930: Films of the stomach immediately and six hours after a barium meal show irregular filling of the stomach with the deformity on all walls of the stomach as shown in previous films. The appearance is practically the same, although in the various examinations the irregularities varied to a slight degree but remained fairly constant in general appearance. There is no obstruction. Stomach emptied at six hours.

Progress Notes.—9/16/30: Patient readmitted.

9/18/30: Patient had severe cramplike pain in epigastrium, pain lasting five to ten minutes. Examination revealed no marked tenderness, no rigidity in abdomen. Pain probably result of pylorospasm.

9/28/30: Patient continues to improve, apparently, on diet. No evident pain in abdomen. No rigidity.

10/4/30: On Smithies régime patient is symptom-free.

10/9/30: Vomited after lunch. Nothing by mouth except water.

10/14/30: Marked clubbing of fingers. No respiratory symptoms, but there is diminished resonance over upper lobes, but no change in breath sounds.

10/16/30: Gastric lavage today for vomiting.

10/25/30: Patient comfortable. Stools still positive for blood.

10/29: Patient says she has vomited and complains that milk upsets her stomach.

10/31: For the past few days since patient has been up in wheel chair she has had recurrence of edema of both legs. Says she has had this for about ten years. No cause can be found to explain.

11/30/30: Patient discharged.

Third admission to Fifth Avenue Hospital, January 2, 1931. Discharged February 16, 1931.

Laboratory.—1/2/31: Stool, blood strongly positive.

1/4/31: Gastric: Blood strongly positive.

1/6/31: Gastric contents following 2 ounces of 7 per cent alcohol: pungent odor, brownish green in color; volume about 60 cc.; blood very positive; lactic acid—trace; no free HCl; total acidity 6.

1/10/31: *x-Ray Examination.*—Films of the stomach show same type of deformity as shown in previous films. This has been classified as multiple polyposis or some type of peculiar gastric lesion which we are unable to identify. The patient is being given a course of deep therapy in an effort to diminish the amount of hemorrhage.

1/17/31: Stool: Blood positive.

2/16/31: Blood very strongly positive.

Progress Notes.—Two weeks before admission patient had severe pains in the abdomen. Stomach lavage showed severe hemorrhage. Has been on Smithies diet three months. Readmitted January 2, 1931. After admission, given gastric lavage. Stomach washed out with plain warm water and then with NaHCO_3 solution. At the last there was a small amount of blood-tinged fluid.

1/15/31: Patient resting quietly. x-Ray therapy being given at forty-eight-hour intervals.

1/17/31: Looks pale today. Blood count shows rise in hemoglobin and red blood cells.

1/23/31: Got deep x-ray treatment today. Says she has felt much better since beginning x-ray treatments.

1/29/31: Deep x-ray therapy, apparently doing some good. Patient apparently improving.

2/9/31: Symptom-free. Has had five x-ray treatments.

2/15/31: Patient markedly improved.

2/16/31: Patient discharged.

Fourth Admission to Fifth Avenue Hospital, June 25, 1931. Discharged July 11, 1931.

Laboratory.—June 26, 1931: Stool: Blood four plus.

June 26, 1931: Physical examination: Tenderness in epigastrium. No mass palpable. Rigidity. Lungs: resonant, breath sounds clear, no rales. Heart: Sounds negative; no murmur; no thrills. Liver: Not enlarged.

June 30, 1931: x-Ray examination: Films of the stomach immediately and six hours after a barium meal show no appreciable change in the lesion involving the stomach. The irregularity varies slightly from time to time but is persistent at the present time. There is no obstruction.

July 11, 1931: Patient discharged.

Case IV.—H. J., age thirty-five years, white male, single, English. Admitted to Fifth Avenue Hospital December 20, 1932. Discharged January 16, 1933.

Chief Complaint.—Pain in epigastrium.

Present Illness.—For the past seventeen years the patient has had a severe colicky pain in the midepigastrium. This pain is quite irregular and may come on at any time for a period of a few minutes to several hours. It may disappear for several years. It has no time relation to food. The pain is cramplike in nature and does not radiate from the midepigastrium. It is relieved somewhat by soda but not by food. Since onset, the patient has had a great deal of gastric flatulence and belching following ingestion of food. For the past week has vomited frequently, being unable to retain any food except boiled milk, eggs, etc. For the past week has had pain in the right lower quadrant. Four weeks ago patient noticed dark blood in the stools in moderate amount. He had hemorrhoids several years ago. The patient has always been constipated. No history of jaundice. Patient was a sailor until 1926 (in tropics most of the time) and has since worked as a painter in New York. Present illness has not increased since he began his work as a painter, but has noticed general loss of strength.

Past History.—Measles. Malaria twenty years ago. Frequent attacks up to 1917. Periodic attacks until six years ago. None since then. Was in Montreal General Hospital for malaria in 1923.

Physical Examination.—Weight, 129 pounds; best weight, 143 pounds. Head, occasional headache. Eyes, sight is good. Ears, negative. Nose and throat, a few colds with sore throats. Mouth, teeth in poor condition.

Cardiorespiratory, some dyspnea, cough, and sputum for several weeks. Some palpitation. No edema. Genito-urinary, no dysuria, nocturia or frequency. Denies gonococcus and lues. Chest, lungs resonant throughout. Liver dulness elevated on right. Breath sounds somewhat harsh. No râles or adventitious sounds in right. Occasional wheezing râle heard in left.

Heart.—Not enlarged to percussion. Left border in midclavicular line. P. M. I. in sixth interspace. No murmurs heard. Sounds regular and of good quality.

Abdomen.—Somewhat distended. Tenderness throughout—more marked in epigastrium. Moderate rigidity makes examination difficult, but there is a suspicion of a mass in the midepigastrium. Liver extends two fingers below the costal margin, one finger to left. Spleen not felt.

Röntgen Findings.—January 14, 1933: Films of the stomach immediately and six hours after a barium meal show marked hypertrophy of the rugae in the cardiac end of the stomach and along the greater curvature almost to the pylorus. There are some changes in the rugae, along the lesser curvature. I am unable to state the character of these changes, but they are quite similar to another case referred by Dr. Goldstein, Mrs. R. (Case III reported above). It was thought that this was some type of polypi in the mucous membrane. There is no obstruction. The stomach is empty at six hours. Films of the gallbladder region after the administration of the dye show the gallbladder filled with the dye. It is within normal limits as to size and shape and there is no evidence of stones.

Progress of Case.—The patient was given dilute hydrochloric acid in increasing amounts without relief of pain. Sippy No. 1 was then tried with partial benefit. It was recommended that a trial series of radiation be given to ascertain whether relief might result from such a procedure. The patient was referred to Metropolitan Hospital, New York City, for trial series of radiation.

SUMMARY

Hypertrophic gastritis is a pathologic entity even in marked contrast to other types of gastritis.

In the only case operated, the stomach was bright red suggesting the possibility of Schumacher's red stomach. On palpation at operation the stomach was soft and boggy, not hard like a carcinoma, or even infiltrated, and not even presenting inflammatory tissue. When the gastric wall was cut the mucosal folds looked like "night walkers" or large angle worms. This appearance was due to the hypertrophic rugae which ran in all directions but principally in circles and obliquely. Actual, untouched photographs of the gross specimen reveal this characteristic appearance.

These hypertrophied rugae are contrasted with normal rugae

and emphasis is placed on the fact that the hypertrophied rugae must be differentiated from normal rugae, especially in cases where the roentgenological findings are to be considered as the basis for surgical procedure.

The microscopical findings are quite characteristic and justify the term, "hypertrophic gastritis." But the microscopical findings are not as startling as the surgical findings of the bright red stomach, or as the roentgenological findings.

Gross and microscopical sections are compared with each other and the microscopical findings are described in detail and illustrated by microphotographs. Hypertrophy of many of the structures is the keynote of the microscopical findings.

The roentgenological appearance of normal rugae is described and illustrated in detail so that those who read this article may not misinterpret normal rugae distinctly shown by some peculiar technic for hypertrophied rugae.

The roentgenological findings of hypertrophic gastritis are graphically but perhaps disgustingly described as having the appearance as though the patient had swallowed a bunch of "night walkers" before drinking the opaque mixture.

Hypertrophic gastritis may involve the entire stomach and yet apparently be limited to the pyloric region because in the pyloric region the rugae are more distinctly shown, especially in cases where the stomach is moderately distended or overdistended in the corporic region. Although there is apparently a diminished lumen in the pyloric region, pyloric stenosis in the true sense of the word is not present. The gastric mixture passes readily through the stomach into the duodenum. Small amounts may remain within the crevices, this retained food acting as an irritant to cause the symptoms of which the patient complains and the roentgenological findings observed in some of the films of each gastric series.

The symptomatology of hypertrophic gastritis is somewhat similar to that of postpyloric ulcer or possibly more resembling prepyloric ulcer when the crater lies in the region of the fan-shaped muscle.

Hemorrhage is not a constant symptom, but in one case

proved a very obstinate and severe symptom, being relieved only by deep roentgen therapy.

Surgical treatment, that is, pylorotomy, was performed in one case with a satisfactory result.

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CLINIC OF DRS. HERMAN O. MOSENTHAL, BENJAMIN I. ASHE, CHARLES A. POINDEXTER, AND R. MACBRAYER

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SPONTANEOUS HYPOGLYCEMIA OCCURRING IN THE COURSE OF ESSENTIAL HYPERTENSION

Case History: Symptoms, signs, and progress of the disease from November, 1919, to death in August, 1932.

Hypoglycemia: Signs, symptoms, and diagnosis.

Hypoglycemia: Functional and anatomical pathology.

Autopsy: Anatomical pathology resulting from persistent hypertension and that related to the hypoglycemia.

Case History.—Symptoms, signs, and progress of the disease from November, 1919, to death in August, 1932. (By Herman O. Mosenthal.)—I thought that for the first clinic this fall we could not do better than to take up a case which we had followed for a long time. This man was interesting from two points of view. In the first place, he was a case of essential hypertension traced from its incipency to death, and in addition, this patient developed spontaneous hypoglycemic attacks which, as you know, are being studied intensively at the present moment and are holding the center of the stage in many clinics.

This man was first seen in November, 1919, when he was thirty-nine years of age. The only previous history of note was that three years before, albumin had been found on a life insurance examination; that was in 1916. In 1919, a trace of albumin was found; however, subsequent examinations failed to reveal any albuminuria. The blood pressure in 1919 was reported as 142 systolic; there were no records of the diastolic.

Physical examination in 1919 showed a very large man, very well developed, 6 feet 2½ inches in height. Although he weighed 209½ pounds he

was not obese for his height. A Wassermann reaction was negative; his blood urea nitrogen was only 12.2 mg. per 100 cc.; examination of the urine showed a specific gravity of 1020. In other words, he had normal renal function and the blood pressure, although 142 had been recorded, proved to be a little higher during the next few months, averaging 156/106.

The blood sugars taken two to three hours after breakfast were always a little low though no symptoms were complained of and an excessive hypoglycemia was not suspected. Between December 1, 1920, and September 29, 1922, they ranged between 80 mg. per 100 cc. and 111 mg. per 100 cc., the actual findings being as follows:

	Mg. per 100 cc.
1920—December 1st.....	100
1921—March 25th.....	80
September 27th.....	80
November 26th.....	90
1922—September 29th.....	111

The blood pressure during this period continued to rise steadily, varying in April, 1925, from 174/110 to 188/132. There were no signs or symptoms except those attributable to the increasing blood pressure. The kidney function remained normal except for an elevation of the uric acid which rose as high as 5 mg. per 100 cc. on May 21, 1924, and remained at about that level constantly, thereafter.

Looking over the history, I find that there were transient attacks of vertigo, headache, and cardiac palpitation, beginning about the middle of 1923. These were not complained of persistently, but occurred only occasionally. In July, 1928, the patient became subject to night-sweats for which there was no explanation. This patient was a physician and when the night-sweating occurred, he was gone over very carefully by specialists in pulmonary diseases. In view of their negative findings, the suspicion of tuberculosis was dropped and it was concluded that these were "idiopathic night-sweats" and of no importance. In reality, I believe they were symptoms of hypoglycemia.

In October, 1928, attacks of cardiac palpitation and tachycardia began to be marked and an electrocardiographic examination showed an auricular tachycardia with a pulse rate as high as 170. About this time, he complained of perspiring a good deal and said he was under considerable nervous strain. The blood pressure had risen to the level of about 202/138. A casual blood sugar gave a finding of 93 mg. per 100 cc.

In January, 1929, there were several attacks of vertigo and the patient himself who, as stated above, was a physician, believed that they were relieved by the taking of starchy food, and diagnosed his attacks as due to hypoglycemia. I think it was a little unusual for these symptoms of tachycardia to be recognized as hypoglycemic manifestations, inasmuch as we had the very high blood pressure to think of as a cause of the tachycardia. Looking back, though, I feel certain that the hypoglycemia had a good deal to do with these cardiac symptoms. At the time, however, we could not quite believe the patient's conclusion that he was having attacks of hypoglycemia.

In February, 1929, there were definite attacks of weakness and hunger

coming on about noon. The blood sugar at 2.20 P. M., after walking thirty blocks, was 79 mg. per 100 cc. By May, 1929, it was necessary for the patient to eat extra food regularly in the morning in order to ward off these distressing attacks of dizziness and hunger.

Throughout the year 1930, the patient adjusted his meals so carefully that hypoglycemic attacks were prevented. He had learned where all the best cafeterias were located and in that way was able to regulate his diet, but by September, attacks of tachycardia became more and more frequent and could not be stopped. On two occasions when there were premonitory symptoms of hypoglycemia, the blood sugar was found to be 77 mg. per 100 cc. and 70 mg. per 100 cc. The patient was afraid to allow the attacks to progress sufficiently far to permit the lowest possible blood sugar readings, because he would suffer too much if the symptoms were not relieved by the eating of food. For this reason, we did not obtain the very low blood sugar figures characteristic of hypoglycemia.

The attacks became more severe until on May 2, 1932, he had a very severe spell with dizziness, marked vomiting, sweating, double vision, and nystagmus. The symptoms and prostration incident to this seizure continued for a week, gradually diminishing during that time. During the height of the illness, the blood pressure was 284/178, the pulse 80 and the blood sugar 50 mg. per 100 cc. I believe he had eaten some food before this blood sugar of 50 mg. was obtained.

Finally, on July 30, 1932, there was another seizure with vomiting, headache, sweating, and dizziness. Two days later, the heart was fibrillating and there was marked prostration. Whether the fibrillation was brought on by the hypoglycemia or was the result of the marked hypertension, or was caused by both, it is almost impossible to say with certainty. The patient did not recover from this attack, but died on August 12, 1932. The final cause of death was a cerebral hemorrhage.

Dr. Poindexter has looked up the findings concerning the functional and anatomical pathology of cases of hypoglycemia and will enlighten us in regard to this interesting subject a little later. In the meantime, Dr. Ashe, who for a long time has been keeping us posted in regard to hypoglycemia, will take up the discussion of the hypoglycemic phases of this case, and hypoglycemia in general.

Hypoglycemia.—Signs, symptoms, and diagnosis. (By Benjamin I. Ashe.)—I should like to discuss the symptoms that this patient manifested while in hypoglycemic shock, and then the symptoms of hypoglycemia in general.

It was by a peculiar combination of circumstances that I was able to observe this patient in three of his most pronounced attacks of hypoglycemia. On the first occasion, March 15, 1929, he was undergoing a sugar-tolerance test. He had been given 100 Gm. of glucose by mouth, and two hours later showed a blood sugar of 150 mg. per 100 cc. which is not below, but rather above, normal. Yet two hours following this elevated reading, he had a blood sugar of 61 mg. per 100 cc. and was complaining of hunger, "inward" trembling and had visible "external" trembling; he was perspiring very profusely; his hands were cold and moist; his blood pressure at this time was 252/184,

higher than at any other time during the tolerance test. These symptoms were relieved by the ingestion of food. Table 1 summarizes the first pronounced hypoglycemic attack which we had observed.

TABLE 1
SUGAR TOLERANCE TEST—MARCH 15, 1929

Time.	Blood pressure.	Blood sugar mg. per 100 cc.	Remarks.
8.45 A. M.	198/144	93	Fasting.
8.50 A. M.	Ingested 100 Gm. glucose.
9.10 A. M.	202/164	142	
9.30 A. M.	202/164	174	
9.50 A. M.	212/166	211	
10.50 A. M.	222/166	150	2 hours after glucose ingestion.
11.50 A. M.	222/164	88	
12.46 P. M.	252/184	61	Perspiration, trembling, hunger, cold hands, nervousness.

The patient felt fairly well until May 2, 1932, when he was on his way in a taxicab to keep an appointment; he was rather suddenly seized with uncontrollable vomiting, marked vertigo and weakness. He was forced to return home; he could not walk unassisted but had to be helped out of the cab, and was put to bed. He complained of vertigo so extreme as to be unable to sit up in bed even long enough to drink orange juice. There was frequent projectile vomiting; he perspired freely; the bedclothes had to be changed frequently; his reflexes (knee jerks, Babinski, Kernig) were normal but he developed a horizontal nystagmus and a definite ptosis of both eyelids. Despite frequent resort to orange juice, he vomited so often as to retain but little of the carbohydrate he ingested. His blood sugar was 50 mg. per 100 cc. Table 2 summarizes this second serious attack of hypoglycemic shock.

The third attack occurred on July 30, 1932, and again began with vertigo, vomiting, and profuse perspiration. On this occasion, with his knowledge of the fact that the previous attack had been due to hypoglycemia, the patient took orange juice and glucose immediately at the onset of symptoms. This may perhaps explain why his blood sugar was relatively normal, 84 mg. per 100 cc., but let it be noted that this was after the ingestion and retention of 6 or 8 glasses of orange juice sweetened with glucose, when a higher blood sugar might be expected. Nystagmus and ptosis of both eyelids were present during this attack as they were in the second. (It is worthy of comment that in May and June, following the second episode detailed above, there had been no residual nystagmus nor ptosis.) In addition, the patient now complained of photophobia. His pulse was not rapid and was of good quality at the onset of this attack; two days later, however, there was a distinct change; auricular fibrillation was suspected and was verified by electrocardiographic examination when the patient entered the hospital. Table 3 summarizes the data with respect to the third attack of hypoglycemic dysfunction manifested by this patient.

TABLE 2
HYPOGLYCEMIC ATTACK—MAY 2, 1932

Date.	Time.	Blood pressure.	Blood sugar mg. 100 cc.	Pulse.	Vertigo.	Vomiting.	Perspiration.	Nystagmus ptosis.	Remarks.
1932 May 2d	10.55 A. M.	284/178	50	80	+++++	+++++	+++++	0	
	4.00 P. M.	226/160		84	+++++	+++++	+++++	0	Blood urea nitrogen 13.
May 3d	9.30 A. M.	200/142		84	+++++	0	0	+++	70 Gm. glucose intravenous.
	11.30 A. M.		106		++	0	0	+++	Began to retain orange juice by mouth.
	6.25 P. M.	204/140		84	0	0	0	+	
May 4th	3.20 P. M.	212/142		84	0	0	0	±	
May 5th	9.20 A. M.	192/128		84	± on walking.	0	Slight.	± or 0	Rare extrasystole.
	12.45 P. M.	202/152	74		Slight.	0	0	0	

TABLE 3
HYPOGLYCEMIC ATTACK—JULY 30, 1932

Date.	Time.	Blood pressure.	Blood sugar mg. % cc.	Pulse.	Vertigo.	Vomiting.	Perspiration.	Nystagmus ptosis.	Remarks.
1932 July 30th	4.20 P. M.		84		++++	++++	++++	0	100 Gm. glucose intravenously.
	11.00 P. M.	188/102		84 reg.	++++	++	++++	0	100 Gm. glucose intravenously.
July 31st	11.00 A. M.			80	++++	0	++++	++++	100 Gm. glucose intravenously; photo- phobia.
	5.20 P. M.				++++	0	0	++++	Retaining orange juice by mouth.
Aug. 1st	11.00 P. M.	212/160		84	++++	0	0	++++	
	7.30 A. M.				++++	++++	++++	++++	100 Gm. glucose intravenously.
	10.30 A. M.	224/148		76	++++	++	++++	++++	Auricular fibrillation.

To recapitulate, the patient during attacks of hypoglycemic reaction manifested a group of symptoms (hunger, perspiration, and trembling) which are the almost invariable accompaniment of hypoglycemia. In addition, he gave evidence of vertigo, headache, vomiting, nystagmus, ptosis, and photophobia, all of which were also due to hypoglycemia but which in a patient with as marked a hypertension as our case manifested, could perhaps have been accepted as the sequelae solely of that elevated blood pressure, *i. e.*, cerebral vascular injury or cerebral encephalopathy. It is with respect to such a differential diagnosis that it becomes necessary to discuss hypoglycemic symptoms in general.

We are led to believe that our patient's neurological symptoms were due to hypoglycemia rather than to hypertension for the reason that vertigo, vomiting, headache, and nystagmus, occur in the course of "insulin shock" even in patients who are not the subjects of essential hypertension. We incline to the view that many symptoms are very often due to unrecognized or unsuspected hypoglycemic, *e. g.*, psychic disturbances, aphasia, transient paralyses, epileptiform convulsions, visual disturbances, weakness, syncope, coma, momentary deafness, difficulty in articulation, uncontrolled spells of laughter or crying, etc. It is becoming daily more recognized that hypoglycemia manifests itself in many bizarre symptoms which were usually thought part of the clinical picture of various well-defined pathologic conditions. Furthermore, in our patient, the symptoms responded favorably to glucose infusion or carbohydrate ingestion. Moreover, the blood pressure was highest at the time that the blood sugar was lowest (see Tables 1 and 2). Elevation of the blood pressure is itself one of the manifestations of one stage in a hypoglycemic reaction. We must conclude on the basis of the blood sugar determinations, the symptomatology, the freedom from residual symptoms in the intervals when the blood sugar was normal, and finally on the basis of the pathology of the pancreas (to be subsequently described) that we were observing attacks of marked hyperinsulinism.

It is logical to inquire, "How does hypoglycemia operate to produce neurological and psychical symptoms?" At least two

theories have been put forth: first, by interference with the nutrition of the brain, second by producing an anhydremia which is accompanied by a cerebral edema. However, final proof of either of these views is not forthcoming.

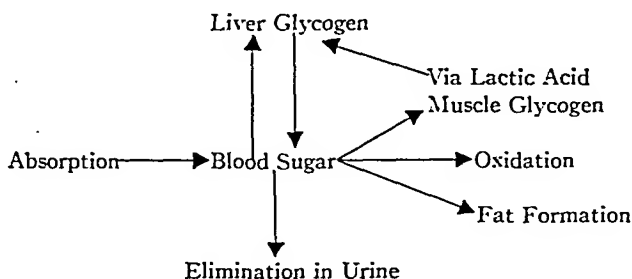
Hypoglycemia.—Functional and anatomical pathology. (By Charles A. Poindexter.)—After looking over the literature relating to spontaneous hypoglycemia, I have very briefly summarized a number of case reports from the English literature and collected them into the following table:

Number of cases.	Age.		Blood pressure.	Heart.
I. Spontaneous hypoglycemia—unknown etiology.				
24	23-60 Av.-40	All apparently relieved by diet or glandular therapy.	All but one normal or below.	All normal but one with paroxysmal tachycardia.
II. Tumors of islands with symptoms.				
7	19-57	Two of 7 removed with apparent cure at operation.	All normal.	All normal.
III. Hypoglycemia with examination of the pancreas.				
4	29-53	3 cases had two thirds of normal pancreas removed by operation—one at postmortem showed hypertrophic islands.	All normal but one. 168/92	Normal. Enlarged heart.

I was particularly interested in these reports to find out, first the effect of the repeated attacks of hypoglycemia on the blood pressure and the cardiovascular system, and second, the functional pathology. The cases reviewed fall rather naturally into three groups. The first group represents those reported because of symptomatology which usually had responded to diet or glandular therapy and in which there was no proof as to the absence or presence of tumors or hypertrophy of the islands of Langerhans. The second group covers those cases of proved tumors of the islands of Langerhans, either benign or malignant, which had symptoms of hypoglycemia. I mention the fact that they had symptoms because there have been cases reported where the finding of a tumor of the Islands was incidental and as far as the authors were able to ascertain, the patients had never had symptoms of hypoglycemia.¹ The third group includes those cases that have had symptoms and the pancreas has been examined anatomically and found to be either normal or showing hypertrophy of the islet tissue. It is easily seen from the table that the groups of cases reported had more of a tendency toward hypotension and normal

cardiac findings than one would suspect from the study of the case presented by Dr. Mosenthal. It is interesting to find that several authors² did report that there was a rise in blood pressure during the attack but apparently no permanent elevation in blood pressure was produced nor was there evidence of permanent damage to the cardiovascular system.

The functional pathology of so-called "spontaneous hypoglycemia," in order to be of help to the clinician, must furnish clues as to where its cause lies. In the first place hypoglycemia or an abnormally lowered blood sugar, with its syndrome of signs and symptoms, is merely an indication of some underlying disturbance. The blood sugar value in itself is not solely an index either of absorption or the functional activity of any one gland. It represents as was³ pointed out some time ago, the balance between the processes of supply and storage on the one hand, and those of oxidation and excretion on the other. This has been very well illustrated by Cori.³



The lowering of blood sugar may therefore be brought about either by a decrease in supply or by an increase in its utilization or its elimination. The decrease in supply may in turn be due to any one or more of a number of causes: (1) Poor digestion in the gastro-intestinal tract.⁴ (2) Deficient absorption from the gastro-intestinal tract. (3) Deficient storage in the liver and muscles.⁵ (4) Too rapid storage.⁶ (5) Inability of the liver to convert the glycogen already stored back into sugar. On the other hand, an increase in its utilization may be effected by an increase in oxidation, and secondly by its elimination in the urine. Once the carbohydrate has been absorbed, two major hormones act upon its metabolism and the regulation of its level

in the blood and tissues. These, as you know, are insulin and epinephrine. An oversupply of insulin such as might be the result either of a pancreatic tumor or hypertrophy of the islands of Langerhans, would result in an increase in oxidation of carbohydrate, an increase in the formation of muscle glycogen and a further inhibition of glycogen breakdown into sugar in the liver, all of these causing a decrease in the blood sugar.

Ordinarily, when the blood sugar falls to a low level, a stimulus to the adrenals brings forth epinephrine in sufficient quantity to speed up the mobilization of glucose from glycogen in the liver. That, plus the increased lactic acid formation in the muscle, part of which is reconverted into glycogen or into sugar by the liver, if the need is great, consequently raises the blood sugar. However, should the continued secretion of insulin be very excessive, as it probably is in hypertrophy or tumors of the islands of Langerhans, a condition is reached where the storage of glycogen is retarded and sugar from glycogen can no longer be formed in sufficient amounts to prevent the blood sugar from dropping to a subnormal level. This, according to the literature, is the most logical explanation for the functional pathologic process. The first group of symptoms that occurs in hypoglycemic attacks, which is probably due in part to the action of epinephrine on the sympathetic nervous system, is not entirely related to the blood sugar level but must depend to quite an extent upon the sensitiveness of the individual's sympathetic nervous system. By that I mean that one person may have marked symptoms with a blood sugar level of 60, and another individual no symptoms until the level has reached 35. When epinephrine is secreted in insufficient amounts, as might occur in hypo-adrenalism, tumors or destruction of the adrenal medulla and in which the compensatory mechanism fails to respond to the action of insulin, we may have a resulting hypoglycemia. Such cases have recently⁸ been reported and it has been noted that individuals suffering from Addison's disease are very sensitive to insulin.⁹

The liver may be responsible for attacks of hypoglycemia but this is not often the case because of the tremendous factor of

safety in this organ. However, in marked instances of carcinomatosis, cirrhosis or poisoning, the liver may be unable to either form or store glycogen, thus resulting in a hypoglycemia.^{5, 10}

That other endocrine glands may play a rôle in the production of hypoglycemia is well known but the mechanism is even less understood than that of insulin and adrenalin. Thyroid overactivity causes an increase in¹¹ carbohydrate metabolism and a decrease in the amount of glycogen stored in the liver, all of which might cause a hypoglycemia. Hypothyroidism may result in hypoglycemia, and such cases have been reported. The pituitary^{12, 13} also has an influence; the posterior lobe secretion is antagonistic to insulin and the secretion of the anterior lobe is supposed to act in the same manner.

I think that it is well to mention the theoretical explanation of the causation of hypertrophy of the islands of Langerhans. We do know that in normal individuals¹⁴ an increase in the carbohydrate in the diet increases the individual's carbohydrate tolerance. It is readily conceivable that a large and constant supply of carbohydrate food over a fairly long period of time might result in hypertrophy of the islands of Langerhans. Under these circumstances if the carbohydrate intake is suddenly diminished an excess of insulin resulting in hypoglycemia, may be anticipated.

The matter of blood pressure changes is also interesting. One would expect that the pressure during a hypoglycemic attack would be raised due to the action of epinephrine¹⁵ and according to Wilder^{15, 16} this actually occurs and is of distinct diagnostic significance.

To sum up I have placed on the blackboard, a slightly modified summary of Gammon and Tenery's¹⁷ which I believe presents quite clearly the functional pathologic disturbances which should be sought for in cases of hypoglycemia:

1. Disturbances in carbohydrate absorption.

2. Disturbances in carbohydrate control either by

- (A) Hyperfunction of the pancreas due to hypertrophy or tumors or abnormal secretion of the islands of Langerhans.

(B) Loss of antagonistic substances, such as, hypo-adrenalism, hypothyroidism, and pituitary dysfunction.

3. From interference of storage of dextrose as glycogen in the liver or muscles or from too rapid a storage.

4. From conditions in which the glucose is rapidly lost through excretion as in severe renal glycosuria.

5. Conditions in which the body's supply of glucose is extensively utilized and not satisfactorily replaced, as in athletic contests, fever, starvation.

Autopsy.—Anatomical pathology associated with persistent hypertension and that related to the hypoglycemia. (By R. MacBrayer.)—The unusual period of study, the aid of the patient himself in making accurate observations of symptoms and signs, the existence of several clinical and pathologic entities and the subsequent studies of this postmortem material and similar clinical conditions warrant the submitting of the entire report of the postmortem examination in conjunction with this case study. This is our postmortem examination, A-76-32, which was performed on August 12, 1932 at 8.45 p. m., one and one-half hours after death.

External Examination.—The body is that of a large, well-developed and moderately obese white adult male of the stated age. The face is somewhat cyanotic as well as the nailbeds. The body is quite warm and no lividity or rigor is present. The scalp, ears, and nose show no abnormality. The pupils are equal, being 6 mm. in diameter. No arcus senilis is noted. The sclerae are clear. The teeth are in good repair. The tongue occupies its usual place in the floor of the mouth behind the lower teeth. No obstruction of the pharynx or upper larynx can be made out on palpation. The thyroid is not palpable. The same is true for cervical lymph nodes. No blood vessels are unduly prominent. Numerous old and recent scars are in each antecubital space. The major peripheral arteries are very slightly palpable. The thorax is symmetrical though slightly barrel-shaped. Usual postmortem resonance is present throughout the thorax except for a very large area of precordial dullness which extends nearly to the left midaxillary line. The abdomen is moderately distended and tympanitic. No masses or organs are palpated. The external genitals, anus, and lower extremities are grossly normal. In the gallbladder region there is a crescentic scar which is 15.5 cm. in length. This is old and well healed without evidences of hernia.

The same is true for a 7 cm. linear scar in the lower right quadrant at the usual site of the appendix. No edema of the ankles is present.

Incision.—The usual Y-shaped incision is made and extended to the symphysis pubis to the left of the umbilicus. The panniculus adiposus varies from 3 to 5 cm. in thickness. The abdominal muscles are dark red in color, well-developed and show no evidence of degeneration. The peritoneal surfaces are pale, smooth, and glistening with the exception of the region of the appendix and gallbladder at which sites there are a few old fibrous adhesions and these organs (appendix and gallbladder) are absent. Approximately 15 cc. of clear straw-colored fluid is in the dependent portion of the peritoneal cavity.



Fig. 19.—A, Patient's left ventricle. B, Patient's right ventricle. C, Left ventricle of 350-Gm. heart. D, Right ventricle from same heart.

The thorax is opened by severing the costochondral cartilages and disarticulation of the sternoclavicular articulations. Each lung falls away from the lateral chest wall in a normal fashion. A rare dense pleural adhesion is present in each apex. In the dependent portions of each lower lobe there is some postmortem change in the nature of lividity. The lungs are everywhere air-bearing and contain an average amount of anthracotic pigment and appear to be moderately emphysematous. The hilic and some mediastinal lymph nodes measure as much as 1 cm. in diameter and are the site of much anthracosis and some fibrosis. A few dense fibrous adhesions are in the interlobar space between the upper and middle lobe. The lungs weigh: right 420 Gm. and left 425 Gm.

A striking feature of the thoracic cavity is the immense size of the heart. The pericardium snugly covers the heart proper. It contains 7 cc. of straw-colored opalescent clear fluid. Its parietal and visceral surfaces are smooth. The heart weighs 930 Gm. The majority of the increased weight is in the left ventricle. The cardiac measurements are as follows: Right auricle 3 to 5 mm., right ventricle 7 to 15 mm., left auricle 2 to 4 mm., left ventricle 25 to 30 mm., bicuspid valve 11 cm., pulmonic valve 8 cm., mitral valve 10.5 cm., aortic valve 7 cm. The latter valve shows some very slight thickening of the valve margins which is apparently due to a slight amount of fibrous tissue increase. The sinuses of Valsalva are patent but about them there is some evidence of sclerosis and definite atheroma. The coronary arteries are visible, palpable and slightly tortuous. On being laid open they are found to contain a slight increase in the amount of fibrous tissue and numerous sub-endothelial atheromatous plaques. No evidence of obstruction or thrombosis can be made out. The ascending portion of the aorta as well as the arch and the entire descending portion is also the site of a moderate degree of sub-endothelial atheromatous change with some sclerotic changes. The intima is smooth and no evidences of thrombosis or ulceration can be found. The heart muscle is of a reddish brown color in its outer half and of a varying pale brown color on its inner half. It is quite firm in consistency.

Neck Organs.—These are not removed because of the limitation of the permit for postmortem. The thymus is not identified in the gross. Thyroid is of usual size and of a normal color and consistency. No nodules or evidences of hemorrhage or malignancy can be made out in the gross. It is not removed. No obstruction to the esophagus, larynx or major neck vessels is made out on palpation and by limited visibility.

Diaphragm.—These organs occupy their usual position and bear a normal relationship to the organs above and below. The right diaphragm is at the lower margin of the fourth rib while the left is at the lower margin of the fifth rib. The subdiaphragmatic space in the region of the liver is free of adhesions and smooth.

Stomach.—This contains a small amount of semidigested food appearing as white small curds. It is moderately distended with gas and has a cubic content much greater than usual. The walls are of usual thickness and of good tone with a smooth and well-preserved mucous membrane which shows no definite vascular changes. The veins about the cardia are visible and palpable though not dilated or thrombosed. The pylorus is nicely patent.

Small and large intestines are moderately distended with gas. The latter contain some semisolid light brown fecal material. The mesenteric veins are moderately distended but without evidence of thrombosis or vascular accident.

The duodenum is very slightly adherent to the gallbladder bed by some dense stringlike adhesions which are easily broken away. The mucous membrane is everywhere intact and well preserved.

Liver.—This organ weighs 2360 Gm. Its edges are moderately rounded. The capsule is slightly thickened but everywhere smooth. The gallbladder is absent and in its bed some adhesions are noted which are attached to the second portion of the duodenum without distortion thereof. Through the capsule of the liver one notes a nutmeg appearance. These pinpoint areas

of dark reddish brown color are surrounded by areas of a dark though definitely lighter brown color. The consistency is somewhat increased. The organ drips much dark red blood from the cut surface. The architecture cannot be definitely made out.

There is an excessively large amount of adipose tissue in the usual sites of major fat depots. This is especially noticeable in the peri- and epicardium, the mediastinal space, the omentum, and mesentery as well as the bed of the pancreas and the kidneys. This adipose tissue is a bright clear yellow color.

Pancreas.—Before stripping away all of the attached fat the pancreas weighs 350 Gm. It is definitely larger than usual though no other gross changes can be made out with the exception of an increased resistance to section in the region of the head. This is noted to be due to some increase in the amount of fibrous tissue. The ampulla of Vater, the pancreatic ducts, and the bile ducts are patulous.

Spleen.—This weighs 330 Gm. It presents the changes of a slight increase in the amount of connective tissue in the trabeculae, some prominence of the walls of the blood vessels on cut section and a dark reddish color which prevents clearly viewing the normal architecture. This is attributed to moderately long-standing passive congestion. The capsule is, in some places, tense while in other places it is slightly wrinkled.

Adrenals.—Each adrenal weighs 20 Gm. About the left adrenal there is some old dark chocolate-colored material which is interpreted as old and semiliquefied hemorrhage. This does not invade the adrenal gland proper which on the cut surface shows a diminution in the intense yellow color of the cortex and a decrease in the amount of the medulla. This latter is a dirty white color, apparently due to some congestion. The source of this periadrenal hemorrhagic material cannot be ascertained. Apparently it is exerting no influence on the adrenal gland but is in the very large amount of periadrenal fat. The right adrenal is not remarkable in the gross.

Kidneys.—The left kidney is removed *in toto* with all of the perirenal fat and in this condition weighs 770 Gm. It is saved for study by perfusion. After perfusion the cut surface shows nice evidence of normal architecture with some prominence of the blood vessel walls. The cortex bears a relationship to the medulla as 1 is to 2½. The pelvis is everywhere smooth and devoid of exudate and calculi. The right kidney weighs 190 Gm. It is the site of what appears to be an old infarct. This is characterized by a depressed wedge-shaped area with the apex toward the pelvis of the ureter. The base of this is at the periphery. In this area the cortex is less than 5 mm. in thickness while the medulla is of about the same thickness. Very little scar tissue is evident. The pelvic fat and the pelvis of the ureter have extended toward this area and in turn the perirenal fat has dipped into this depressed area in the cortex. At the base, this depressed area of decreased renal tissue measures 2.5 cm. The capsule strips without difficulty to leave a smooth surface except in a rare area where it tears the kidney substance. On section the vascular channels throughout the cortex and medulla stand out as reddish brown areas. The ureters and bladder are not remarkable. The urethra is patent.

and endocardium the muscle fibers are more faintly stained, decidedly more granular, more swollen and the site of cloudy swelling. In this region there is greater variation in the appearance of the nuclei and a greater amount of fragmentation of the fibers. No increase in connective tissue or cellular infiltrations is seen. The endocardium is well preserved and intact. The myocardium immediately underlying the endocardium shows even more degeneration and less visibility of striations than seen elsewhere. Also in this region near the endocardium the nuclei vary more in staining quality and size than elsewhere.

Left Ventricle.—The endothelial cells lining the endocardium are well preserved. The endocardial and subendocardial areas are thickened by a slight amount of edema, a slight increase in the amount of connective tissue, and some infiltration of plasma cells. The muscle fibers are very large and contain large nuclei which vary somewhat in shape and staining intensity. In some areas there is much of the lumpy disintegration while in other areas just beneath the endocardium there is excellent preservation of the linear and cross striations. The myocardium appears very cellular due to the numerous endothelial cells lining the capillaries—some of which show much proliferation. Rarely a small amount of fine light brown pigment is at the poles of some nuclei. The vascular and connective tissue stroma is everywhere slightly increased. Rarely one finds an area of dissolution of muscle fibers which have been replaced by fibrous tissue. Occasionally some muscle fibers show fragmentation. Along even some of the smaller trabeculae there is more adipose tissue than usual. Everywhere the muscle bundles and some fibers are widely separated by nonstaining spaces. Apparently this is attributable to some edema, perhaps to marked passive congestion with the virtual collapse of the vascular channels when the blood was removed from the organ. The larger and smaller branches of the coronary arteries are quite cellular, due to an increase in the number of endothelial and muscle cells. In the larger branches some areas of hyalinization are present. Here again lumpy disintegration and some edema is present in the muscle walls along with an increase in number of fibroblasts. About some of the larger blood vessels there is much edema and a greater fragmentation and loss of the muscle fibers than elsewhere. In such areas the muscle fibers appear atrophic rather than hypertrophic. Another section of the myocardium shows the endothelial cells of the endocardium to be lacking in some places and in other areas to have attached to them some small bits of fibrin-like material. Immediately beneath this layer of endothelial cells there is a slight increase in the amount of connective tissue and the muscle fibers appear hyalinized, edematous, and slightly vacuolated. In other areas of this same locus several collections of small lymphocytes are noticed. Some old blood pigment appears in some small vascular sinuses.

Aorta and Blood Vessels.—In the aorta and numerous other blood vessels, especially the renal and splenic arteries, there is a marked thickening of the intima due to a small amount of edema and a large amount of fibrous tissue increase. In some places this is 1 mm. in thickness. In some areas in the aorta the intima is roughened and absent. Immediately beneath the intima the muscle fibers are pale and very few nuclei are seen. Other muscle areas

are hyalinized. The vasovasora are very cellular and about some of them in the adventitial zone there are collections of small round cells and some fibroblasts. The external elastic membrane is also very cellular and admixed with the elastic tissue there is a definite increase in the amount of fibrous tissue. The intimal changes are exceptionally prominent in the renal arteries which were fixed by perfusion under pressure.

Liver.—The capsule is thickened to approximately 1 mm. due to some edema and much increase in old connective tissue. The peritoneal surface shows absence of some endothelial cells and at these sites there are small attachments of fibrin. In some areas this is partially organized. Throughout the substance of the liver the sinusoids and other vascular channels are greatly distended with whole blood. There is a slight increase in cellularity and a moderate increase in the amount of fibrous tissue in the perilobular areas of Glisson's capsule. The cells lining the bile ducts are well preserved and prominent. In the main the nuclei of the liver cells are well preserved. There is some variation in size and staining intensity. The cells themselves show some fine granularity and a questionable edema. Scattered throughout some few cells have their cytoplasm completely replaced by a fatlike material. This appears to be fatty degeneration. The polynuclear leukocytes in the sinusoids are increased in number. The central vein is moderately dilated and within the lumen there is some old blood pigment. Special glycogen stain shows an exceptionally small amount of this material present.

Spleen.—The capsule is thickened and made up of very dense and slightly hyalinized fibrous tissue. The same is true though to a greater degree of the trabeculae. The walls of the blood vessels are very greatly thickened and have much increase in fibrous tissue which is largely hyalinized. Here and there some areas of degeneration are noted within the walls of these blood vessels. The splenic corpuscles are moderately hypoplastic. Except in the areas of the splenic corpuscles the lymphocytes are decreased. The stroma is made up in the main of vascular channels and reticulum cells. There is much old and recent blood pigment within and without the cells. All vascular channels are moderately distended with red blood cells.

Adrenal Glands.—A marked increase in the amount of fibrous tissue in the capsule is noted. In some places this measures 1 mm. in thickness. The blood vessels in this area show the same sclerosis as described for the blood vessels elsewhere. Small trabeculae of fibrous tissue extending into the glomerular zone of the cortex are more pronounced than usual. There is some edema in the glomerular zone. Throughout the cortex which appears at least comparatively increased in amount the cells are well preserved and in some areas hyperchromatic and are in large collections resembling adenomatous formations. Throughout the cortex there is some decrease in the amount of lipoidal material. In the inner portion of the vesicular zone the cells are quite edematous and show some fine and coarse granularity. In other areas some cells are slightly vacuolated. In these sections there is a very small amount of medullary substance. In the medulla there is much edema and the veins are greatly distended. In and about the cells there is much brownish pigment apparently due to chronic passive congestion. To a lesser degree this edema is present in the inner zone of the cortex. The vascular

channels in the medulla are greatly distended with old and recent whole blood. In a few areas old hemorrhage apparently has taken place.

Kidneys.—Two vascular changes are noted, namely, marked arterial sclerosis of the large and small vessels. In their walls in some areas hyalinization is present. The other change is a marked degree of chronic passive congestion. The glomerular tufts and Bowman's space show various degrees of degeneration and inflammation from the normal to complete sclerosis. In some of the spaces a few red blood cells and a rare polynuclear leukocyte are noticed. In other areas there are numerous adhesions between the glomerular tufts and the outer wall of Bowman's space. Some tufts are very small, others are exceptionally large. In Bowman's space in some areas a moderate amount of very finely granular, homogeneous, and nonorganized material is present. This seems not to be cellular debris but rather a transudate. The renal epithelium in general is very poorly preserved, part way due to antemortem and part way due to postmortem changes. The latter are characterized by desquamation of the cells into the lumen and a moderate pyknosis of the nuclei. The former changes are in the nature of some atrophy, some granular degeneration and some edema. This degeneration has progressed to the point that some of the uriniferous tubules show a complete loss of epithelial lining in a few areas. The tubules also contain much of the above described homogeneous slightly blue-staining material. Some of the cells show vacuolization. With difficulty are distinct cell outlines made out. In other areas several adjoining cells contain no visible nuclei. Throughout the cortex and medulla—more so the latter—there is a marked increase in the connective tissue stroma. Here and there in the connective tissue stroma there are some small collections of lymphocytes along with a rare plasma cell and eosinophilic leukocyte. These areas in no wise resemble abscess formation. As a result of this the collecting tubules appear very small and slightly atrophic.

Prostate.—The glands are more numerous and some larger than usual and show a moderate amount of adenomatous proliferation. Withal the lining cells are faint staining and appear atrophic. In many instances the lining cells have desquamated (doubtless due to postmortem change) into the lumen of the glands. No inflammatory reaction is noticed. The stroma shows a marked increase in the amount of the muscle element. A few corpora albicantia are noted.

Pancreas.—The pancreatic tissue is unusually compact and cellular. In some instances the cells of the acini are not in proper order though no evidence of malignancy is present. A moderate amount of hyperplasia and some hypertrophy of these gland cells is noticeable. The acini vary greatly in size and shape. The island tissue by rough measurements is greatly increased both as to number of the islands and size of the islands. By measurement of numerous islands, the average diameter is 215 micra which is about 75 micra greater than is accepted for the usual diameter of normal-sized islands. In some areas these have a slightly adenomatous arrangement and a limiting wall or outline is not definitely determined. Here and there the cells of the islands appear to be continuous with those of the acini. In the larger islands there is a network of moderately distended capillaries which divide the island

tissue into smaller islands or adenomatous-like areas. The pancreatic duct shows a marked increase in the amount of fibrous tissue in its wall though careful search fails to reveal the presence of any active chronic inflammatory lesion. The blood vessels are markedly sclerosed as described for other organs.

Anatomical Pathologic Diagnosis.—The ascertaining of the exact nature of the morbid anatomy seen at the postmortem table is often difficult and at times impossible because of the limitations of our technical procedures and knowledge. Even more difficult becomes the arrangement of discerned facts and opinions in chronological order and in such relationship with each other as will portray the evolution and nature of the disease or diseases present. The case in hand presents several such difficulties—each of which constitutes opportunity for further study. Our present conception of the diseases and in part their evolution is expressed in the protocol:

Primary.—(A) Arteriolar sclerosis of kidneys.

Hypertension (clinical).

Cardiac hypertrophy.

Atherosclerosis of aorta and coronary arteries, generalized arteriosclerosis.

Chronic diffuse nephritis with superimposed granular degeneration, edema and congestion; infarct of kidney, right, healed.

Chronic inflammation, localized fibrosis and diffuse degeneration of myocardium.

Chronic passive congestion, granular, and fatty degeneration of liver.

Chronic passive congestion and hypoplasia of spleen.

Cerebral hemorrhage (clinical).

(B) Anthracosis, fibrosis, and chronic passive congestion of lungs.

Chronic inflammation of pleurae with fibrous adhesions.

(C) Hypertrophy and hyperplasia of pancreas.

Hypertrophy and hyperplasia of islands of Langerhans.

Congestion, granular degeneration, and hemorrhage of adrenal glands.

Secondary.—(A) Varices of spermatic cord, bilateral.

Diffuse hypertrophy of prostate.

Periadrenal hemorrhage (old).

(B) Absence (operative) of gallbladder and appendix.

Postmortem changes in prostate, lungs, intestinal tract, and kidneys.

Note.—No pathology attributable to or usually associated with disease of the gallbladder and appendix is as such identified.

Discussion.—The heart is unusually large—as you can see. The left ventricular hypertrophy is an extreme degree and elsewhere there is a symmetrical hypertrophy. This picture is very characteristic of aortic valve disease or hypertension—more so the latter with competency of all valves. Our not seeing this more often is attributed to the imbalance of factors which does not permit such a long period of time in which to gain this size. The weight of this heart, 930 Gm., is only a little below those mentioned by McCrae though not nearly so large as the one reported by Duller to weigh 1440 Gm. In this heart are the evidences of both old and recent inflammation and degeneration. As could be anticipated from the advanced degeneration of the coronary arteries, the degenerative changes are the most recent and extensive. This permits the opinion that the hampered blood supply in this

case was a factor in limiting the hypertrophy. Absence of the usual cardiac dilatation in such cases is accounted for by the advent of the cerebral accident which precluded progression of the cardiac pathology to enforced dilatation. This accident also contributes to the evidence that there is a greater degree of degeneration in the arteries than in the heart.

The kidneys present their oldest changes in the arterioles. Present concepts of pathology are that such sclerotic changes are to be anticipated in unexplained hypertension and that whenever the compensatory elevation of blood pressure is noted to be increasing as time elapses, one can expect to find a severe degree of progressive arteriolar sclerosis at the postmortem examination. Supervening on this change in a manner and for reasons as yet largely theoretical are seen the changes in the renal epithelium and supporting stroma constituting chronic diffuse inflammation of the kidney. A large part of the subsequent changes can, however, be attributed to the interference with the vascularity of the cortical zone of the kidney resulting from diseased arterioles derived from the arcuate arteries. The prolonged life in this case could well be due to a nice balance between the compensatory hypertension, the compensatory cardiac hypertrophy and the progressive kidney pathology.

The adrenals deserve close scrutiny in this case because their products are so intimately connected with some phases of metabolism, and the virtual absence of glycogen in the liver causes one to glance adrenalward. At present, however, there is insufficient evidence to warrant other than speculation in this field. Further studies and considerations of these glands in chronic hypoglycemia may elucidate some angles of or clinical pictures seen in this state.

At present there is very little to be added to our gross and microscopical descriptions of the pancreas. The generalized arteriosclerosis is present in this organ though no morbid changes of the parenchyma attributable thereto are observed. Also, no evidence of ascending pancreatic duct pathology is seen as is noted in some cases of associated gallbladder and biliary tract disease. We can state, however, that some findings commonly associated with hyperfunction of cells and organs are present in this organ. A further study of this pancreas is now in progress and will be reported upon at a later date.

Summary (By Herman O. Mosenthal).—We have tried to give you the significant clinical and pathologic findings in a somewhat unusual case of essential hypertension and spontaneous hypoglycemia. Thanks are due to the great amount of trouble Drs. Ashe, Poindexter, and MacBrayer have taken in carrying out a thorough report on the various aspects of the problems involved.

In concluding I would like to draw your attention particularly to certain points. This patient presented an unusual opportunity of observing a case of essential hypertension from its incip-

iency to its fatal termination. The duration of the essential hypertension was about thirteen years. There was a constant, progressive rise of the blood pressure. In 1925, that is seven years before death, the diastolic tension had reached a level of 130 mm. of mercury. It is usually believed that with this level of blood pressure, the average anticipation of life is about two years. This, as a rule, is correct but there are many exceptions, as in this instance, in which the duration of life was seven years, that is a considerable period above two.

The cause for this comparatively favorable prognosis apparently lay in the fact that the patient's heart muscle was able to respond by hypertrophy in a very satisfactory way, and maintain normal circulation in the face of the obstacles which it was necessary for it to overcome. During his whole life, this patient carried on fairly strenuous work. It is well worth while bearing this in mind when treating cases with high blood pressure because we are too prone to shelter these patients to an unwarranted degree. That is, physical exertion and nervous strain within limits do not appear to have any detrimental effect but, to my mind, rather a beneficial one. Certainly in this instance, they did not shorten the span of life but I believe rather served to lengthen it.

Dr. MacBrayer has called your attention sufficiently to the changes in the blood vessels and in the heart, which have developed here to such a marked degree because of the long duration of the hypertension.

As we look back upon the subjective complaints, the hypoglycemia apparently had been in existence for nine years. The symptoms constantly increased in severity, and finally became so marked that they certainly favored, if they did not cause, death. At first only vertigo and excessive sweating were complained of. Of course, it is wrong to diagnose every case with dizziness or an excessive perspiration, as being the subject of a subnormal concentration of dextrose within the blood, but one lesson that we can derive from this study is that this possibility must be borne in mind when such symptoms present themselves. Also, as we review the subsequent history, it is

apparent that cardiac palpitation and tachycardia must be regarded in a similar light, although one cardiac specialist absolutely refused to consider these signs and symptoms as indicative of hypoglycemia. The duration of nine years, from mild doubtful hypoglycemic attacks to very severe ones, furnishes a possible standard by which the progress of events in these cases may be judged.

The cause for the production of a low blood sugar apparently was the hypertrophy of the pancreatic tissue. Operation in this patient was out of the question because of the presence of high blood pressure and the effect that this had had upon the heart. As I understand the situation from others, the policy in regard to the surgical treatment of possible changes within the pancreas that bring about a lowering of the blood sugar, is to wait as long as possible and only seek relief by surgery when the disturbance has advanced so far that life is no longer bearable. Exactly how this idea should be regarded as a formal rule seems rather questionable. Each case certainly should receive individual consideration. Progressive increase of the severity of the symptoms over a period of time would naturally point to surgical relief as the only available means of cure or alleviation.

The treatment of the hypoglycemia indulged in for this patient was not thoroughly successful. That is, the feeding of starches at frequent intervals in order to raise the blood sugar may have brought about a further hypertrophy of the pancreatic tissue. This is an open question but one that deserves study. During the last days of the illness, a high fat diet served to maintain the blood sugar at a normal level. Possibly such a diet instituted earlier would not have favored the hypertrophy of the pancreas, as the feeding of starches may have caused.

There are only two further points that seem to me especially noteworthy. The first of these is that the hypoglycemic symptoms occurred at a comparatively high blood sugar level. For instance, with a glucose concentration of 61 mg. per 100 cc. they were very marked. We see many patients with blood sugars of about this value who show no symptoms. It is well known that the individual reaction to the blood sugar concentration

plays a very big rôle and that it must be given due consideration in every instance.

The second is that the blood pressure rises very markedly as the blood sugar drops. Attention has been called to this frequently and has been beautifully shown in this patient by Dr. Ashe. This finding is of great value in making a differential diagnosis in comatose patients, between insulin overdosage and hypoglycemia on the one hand, and other conditions associated with unconsciousness.

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CLINIC OF DR. HAROLD E. B. PARDEE

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EXTRACARDIAC CONDITIONS SIMULATING THE ANGINAL SYNDROME

RECENT studies have led more and more definitely to the conclusion that what was known as angina pectoris is almost always due to disease of the coronary arteries with varying grades and degrees of occlusion. With the minor grades these symptoms appear especially on effort. When an occlusion is complete and sudden the attacks recognized as due to coronary thrombosis will ensue. Angina pectoris is, by definition, a suffocating sensation in the chest, but the term has become strongly associated with a special variety of pain, particularly a heavy, constricting, painful sensation in the retrosternal region with radiations to the left shoulder and arm. Many variations of this pain are found, as was described in a clinic published in March, 1921,* it is not the purpose at present to dwell upon this phase of the problem.

A chronically narrowed coronary may give rise to pain or discomfort in the course of physical effort or mental excitement. An acute coronary closure will give rise to pain or discomfort accompanied by a degree of prostration and weakness which is a prominent feature of the patient's condition. The pain in the latter case is usually severe, although in certain patients it may be quite mild.

It is a well-recognized fact that certain other diseases of the heart may give rise to similar anginal pain and it is also recognized that diseases of other nearby organs may give rise to a group of symptoms very similar to the anginal syndrome and

* THE MEDICAL CLINICS OF NORTH AMERICA, March, 1921.

only to be distinguished from it by a careful study of the symptoms and of the physical signs to be found in the heart and in the nearby organs.

Among the cardiac diseases other than coronary narrowing which can give rise to the anginal syndrome, it is necessary to mention most prominently syphilitic aortitis, which is very liable to involve the coronary orifices and cause a disturbance in the coronary circulation. Rheumatic disease of the aortic valve with deformity of the sinuses of valsalva which involves the mouths of the coronary arteries can cause similar symptoms. Paroxysmal rapid heart action due to auricular fibrillation, auricular flutter, or paroxysmal tachycardia can also give rise to this symptom complex because of the resulting defective circulation in the myocardium.

When the symptoms are typical and there are definite physical signs of cardiac disease the diagnosis is a simple one. If the patient presents the anginal syndrome in a typical form even without definite physical signs to indicate pathologic changes in the heart it is possible to make a diagnosis of cardiac disease. With atypical symptoms a diagnosis of cardiac disease may be made if definite signs of heart disease are found, as was discussed in the clinic of March, 1921. If the symptoms are atypical and the physical signs negative then we must consider all the various causes of pain in this region and must be on the alert for a suggestion that some other organ than the heart may be the site of the disturbance.

The cases to be presented will illustrate several phases of the diagnosis of the cause of precordial pain. To illustrate all of the difficulties encountered is much beyond the possibility of this clinic but the important common sources of confusion can be indicated.

Case I is a man forty-eight years of age who was taken sick nine months ago with what was diagnosed as influenzal pneumonia. He was in bed with this for about twelve days and made an uneventful recovery. On the first day up he tried to move his morris chair and felt a severe constricting pain across the precordium which lasted for half an hour and made him feel very weak. He remained in bed for a week longer and then was convalescent, but on going out for a walk for the first time felt a similar pain. Three months

later he woke one night with a severe sense of dyspnea and a squeezing sensation in the chest. He had to sit up for half an hour, before this subsided. This recurred for several nights, gradually becoming less severe. After these attacks he began to have shortness of breath on walking three or four blocks and after from five to seven blocks he felt a dull retrosternal pain. Once, on attempting to park a car in a difficult place, the pain reappeared in a rather severe form. It subsided promptly when the effort was over.

The physical examination showed a normal appearing man without pallor or cyanosis. The pulse was of medium size and of good force. The blood

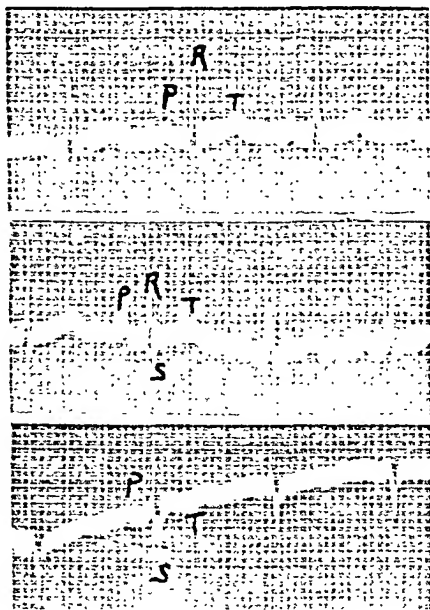


Fig. 22.—Electrocardiogram of Case I shows a normal sinus rhythm with normal auriculoventricular conduction time. P-R measures 0.16 second. The QRS group shows left axis deviation with R larger in lead 1 than in lead 2 and a definite S wave in lead 3. The T wave is upward in leads 1 and 2. There is nothing about this electrocardiogram to suggest myocardial abnormality.

pressure was 110/82. The area of cardiac dulness was not enlarged. The heart sounds were normal and no murmurs were heard. The lungs and abdomen were negative except that the vital capacity of the lungs was only 70 per cent of the average for a man of his height.

The x-ray examination of the heart showed it to be of somewhat increased size; its movements were normal and the aortic arch presented a prominence to the left of the sternum as it turned back into the descending

portion. This is a common appearance with aortic atheroma. The electrocardiogram was normal in every respect except for a moderate degree of left axis deviation of the QRS group, a finding which in itself does not indicate cardiac disease but only suggests hypertrophy of the left ventricle.

This patient has no physical signs of heart disease except slight enlargement. His case is presented today because the symptoms are so typical of the various manifestation of the

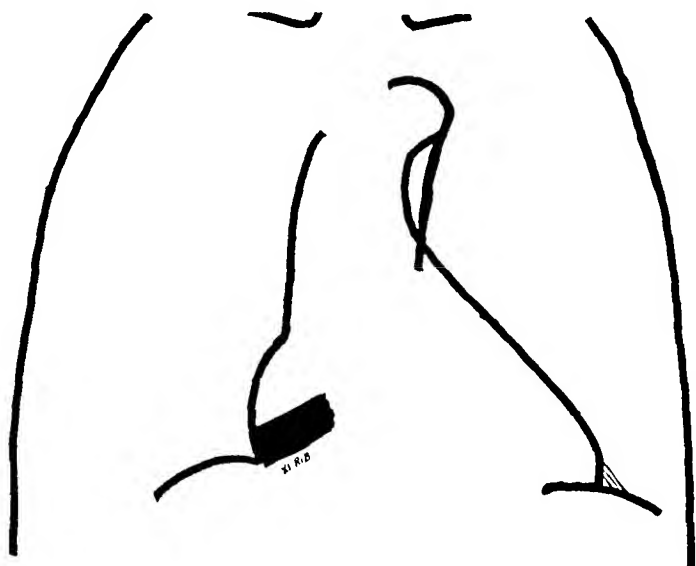


Fig. 23.—Orthodiagraphic tracing of Case I. The right side of the diaphragm is very slightly above the left and both are at the level of the eleventh rib posteriorly. The transverse diameter of the heart measures 13.2 cm. which is 1 cm. more than the average for one of his height, weight, and age. The heart lies transversely upon the diaphragm. The aorta is not dilated and appears normal except for the prominence toward the left of the transverse portion of the arch.

anginal syndrome that, especially in view of the combination with paroxysmal nocturnal dyspnea, we are compelled to make a diagnosis of arteriosclerosis of the coronary arteries with anginal syndrome, and, owing to his inability to exercise without dyspnea and his reduced vital capacity, we can also diagnose slight cardiac insufficiency. The normal electrocardiogram suggests that pathologic changes in the myocardium have not yet

reached an important degree. The symptoms are typical and point definitely to the heart despite the practically negative examination.

Case II.—A woman fifty-five years of age stated that one year ago she began to have intermittent sharp pain in the region of the left breast and an aching sensation in the third and fourth intercostal spaces at the left midclavicular line. This became worse on walking and gave rise to a sensation of shortness of breath. At times she had a gnawing pain in the shoulder radiating down the left arm and which was worse on walking. These symptoms continued until two months ago when she had a feeling in the throat and in the chest as of a sudden pressure. The pulse was noticed to be intermittent at the time that this sensation occurred. It occurred irregularly and with variable frequency. The pain in the region of the left breast continued intermittently and would radiate through the left subscapular region. It often came in the course of walking or during such efforts as light housework or with excitement, and would often radiate down the left arm and into the thumb. At one time there was an attack of pain beneath the lower sternum radiating to the left breast and the left scapular region. There was a pressure sensation as if she had swallowed something too large. This attack lasted several hours, the pain coming and going from time to time. There was absolutely no prostration associated with this attack. She was able to go out during its course but found that it was worse on walking. It was not worse on deep breathing or on movements of the trunk.

Physical examinations showed a well-nourished woman of somewhat nervous type, slightly pale. The pulse was 80 per minute, of medium size and of good force. The blood pressure was 186/80. The area of cardiac dullness was not enlarged. The first heart sound at the apex was somewhat increased, the aortic second sound showed a slight ringing quality such as is found with atheroma. The lungs and abdomen were negative. There was very slight tremor of the hands.

The x-ray examination of the heart showed no enlargement. The aortic arch, however, was somewhat tortuous in its appearance as is found with slight atheroma. The electrocardiogram showed a normal rhythm interrupted by occasional premature beats arising in the auricles. The electrocardiogram showed no abnormality of the ventricular waves except a marked left axis deviation which would indicate a definite hypertrophy of the left ventricle.

Here the site of the pain is atypical. It is in the region of the left breast instead of the usual retrosternal region. Its radiation to beneath the scapula is atypical in spite of the fact that at times it radiates down the left arm and that it is at times aggravated or precipitated by effort or by excitement. It is also atypical in the fact that it sometimes appears without relation to effort and lasts for a considerable number of minutes or hours without accompanying prostration. The patient showed a ringing aortic second sound as is common with hypertension but in the fluoroscopic examination there were evidences of atheroma of the aorta. This is, of course, close to the mouths of the coronaries and the marked left axis deviation of the electrocardiogram

and the auricular premature beats indicated that the heart was not entirely normal, that it was probably in some measure affected by the arteriosclerosis which accompanied her age. On the other hand, the atypical character of the symptoms led to further questioning and it was found that they showed a very definite relationship to cold and damp and were often aggravated by sitting in a draft. The patient also had occasional vague pains in the joints.

An x-ray of the dorsal spine was made and showed osteo-arthritic changes in the cervicodorsal articulation and marked osteo-arthritic changes in the third, fourth, fifth, and sixth dorsal vertebrae. It was considered in view of these findings that the patient was suffering from osteo-arthritis of the dorsal vertebrae with irritation of the dorsal nerve roots as the cause of the pain in the chest and arms. It was considered possible that she might have very slight arteriosclerotic changes in the heart, but no more than might be considered normal for one of her age and that the heart was not responsible for her symptoms except those which were noted in connection with the intermittent pulse, and were a result of the premature beats. Whether these premature beats themselves are an indication of an arteriosclerotic process in the myocardium, or whether they are due to irritation of the dorsal nerve roots bringing sympathetic fibers to the heart must be a matter of debate.

During the course of the five years that this patient has been under treatment three abscessed teeth have been removed. Salicylates, atophan, and cyncophen, have been given from time to time for the pain and have had definitely beneficial effect. The local applications of heat over the spinal column have also been helpful. The patient has shown gradual improvement, although of late there has been an increase of the pain on bending the trunk, a feature which was not present in the early course of the disease. At the times when the pains are worse she is apt to have more of the thumping of the heart, and irregularity of the pulse, suggesting a likelihood of a direct relation between the osteo-arthritis and the arrhythmia.

In this case the atypical symptoms gave an indication that the disease under consideration was not arteriosclerosis of the coronary arteries; the positive evidence of the spinal x-ray examination confirmed this opinion.

Case III.—A woman, thirty-two years of age, complained of shooting pains over the heart. In the winter of 1922 she was troubled by a dull aching pain in the left side of the chest, low in the shoulder, at times radiating up into the neck below the ear and down the left arm to the fingers. This dull ache was aggravated by movements of the arm and was associated with tenderness of the deep tissues. It was diagnosed as neuritis and continued until three and a half years ago when, following treatment by six x-ray exposures at weekly intervals, radium bath and diathermy, the pain practically disappeared and has not returned. Sixteen months ago her father died of heart disease and for several months the patient was troubled by palpitation at night. Her heart would beat rapidly and kept her awake. This trouble, however, improved gradually and eventually disappeared. Nine months

ago she began to have shooting pains over the heart which felt like a spasm. These came without any relation to effort or excitement. They increased in frequency and she became worried about them. Eventually the pain appeared almost daily. Once, after playing golf on a hilly course, she felt very short of breath and this sensation lasted for most of the day. This and certain occasions when she has been dancing are the only times that she has thought that her wind was not normal. For two months she has had a dull aching pain beneath the left breast. This in addition to the shooting pain which had been bothering her for seven months previously. The sharp pain would now radiate to the left shoulder and left side of the neck and would

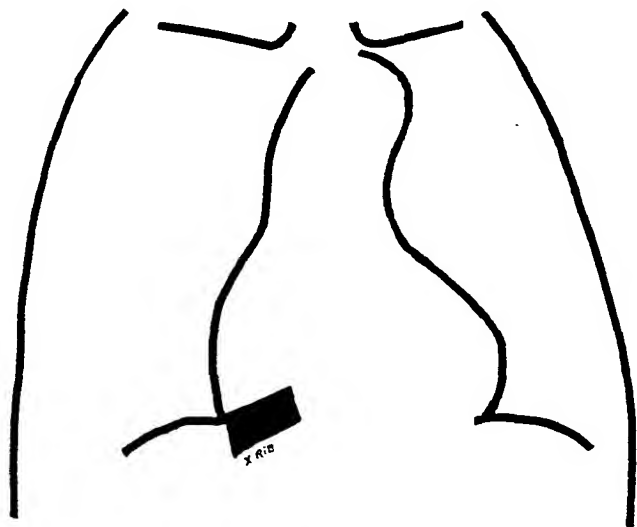


Fig. 24.—Orthodiagraphic tracing of Case III. The left side of the diaphragm is slightly higher than the right side and is more horizontal, being pushed up by gas beneath it. The diaphragm is at the level of the tenth rib posteriorly. The heart lies rather transversely upon the diaphragm, its transverse diameter being 11 cm. which is the average for one of her height, weight, and age. The aorta is not dilated and appears normal.

last longer than formerly. She feels it more on days when she is more active than on days of relative rest, but it does not arise as a direct sequence of any effort.

Examination showed a normal appearing young woman. Her pulse was 84 per minute and small. The blood pressure was 124/74. The peripheral arteries were not palpable. The area of cardiac dulness extended 1.8 cm. to the left of the midclavicular line, but the orthocardiographic tracing did not show cardiac enlargement although the heart was lying quite transversely on a high diaphragm. The heart sounds at the apex were normal and likewise at the base, and no murmurs were heard. There was an area of tenderness in the precordium over the third and fourth left intercostal spaces and over the

fifth intercostal space in the region of the apex beat. Examination of the lungs was negative except that the vital capacity was 85 per cent of the average for one of her height. The electrocardiogram showed a normal sinus rhythm with a left axis deviation of QRS. The QRS of lead 3 was of the M type and the T wave in this lead was somewhat inverted. There was, however, no significant abnormality to indicate myocardial changes. It was noted that the left dome of the diaphragm was at the same level as the right side, and that there was a large accumulation of gas in the stomach so that this was distended and almost entirely filled the left dome of the diaphragm. It is possible that this pushing up of the diaphragm accounts for the reduction in the vital capacity of the lungs, so that we do not feel called upon to refer it to cardiac insufficiency.

In this patient the palpitation and perhaps the unusual shortness of breath are suggestive cardiac symptoms but the heart is quite normal on examination. The pain has not at all a typical anginal character nor does it have its origin in immediately preceding effort. The pain is in the region affected by the former neuritis and the possibility of a return of this or a late manifestation of the old process must be considered. There was nothing to support this diagnosis, however, as the sensibility along the nerve trunks and the reflexes in the affected area were normal. We must consider the fact that many of those who have large gas accumulations under the left dome of the diaphragm are found to suffer from pains in the left hypochondrium, and in the neck, and in the left scapular region occasionally with radiation down the arm. Pain from this cause is of the referred type and arises from radiation of the afferent impulses entering the spinal cord along the diaphragmatic nerves. A diagnosis of pain from subdiaphragmatic gas accumulation seems indicated in this case because of the very great distention of the stomach with air. Quite severe attacks of pain may occasionally result from the kinking of a gas-distended colon, there may be a quite severe pain below the left breast with radiation to the side, neck, and arm. Such pain is not accompanied by the prostration which would be expected of pain of similar severity due to coronary thrombosis, and therefore, should not be difficult to distinguish from such an attack.

Case IV.—A woman, fifty-six years of age, has complained of severe pain beneath the left breast radiating to the back and down both arms. For

years she has been subject to "indigestion" with belching after meals and a sense of epigastric fullness. Eight years ago she began to have attacks of diarrhea which would last two or three days and be aggravated by a pain throughout the left side of the abdomen. Five years ago she began to have pain beneath the left breast which radiated around into the axilla. This was a sort of ache and was present most of the time. Sometimes it would shoot through to beneath the scapula and at times would be accompanied by a pain in the left arm and by a numbness and tingling of the hands.

Examination at this time showed a woman somewhat overweight, of stocky build, with somewhat florid facies; the pulse was small, the artery wall was not thickened, the blood pressure 200/90. The area of cardiac dullness could not be determined because of the large size of the breast, but the orthodiagraphic tracing showed a transversed diameter of the cardiac shadow slightly above the average and a definitely increased bulging of the left ventricular border. At the apex the first sound was normal, and was followed by a definite, long, blowing systolic murmur. The aortic second sound was slightly ringing and there was a definite, long, hard systolic murmur heard there. The electrocardiogram was normal in every respect. The lungs were negative. The abdomen showed some general tenderness. There was no edema of the extremities. At this time a diagnosis was made of chronic colitis with pain due to subdiaphragmatic irritation. Under treatment by appropriate diet and the administration of bismuth there was considerable improvement. The blood pressure continued in the neighborhood of 165/90 and the patient continued to have occasional aching pains beneath the left breast.

Two years ago the patient had an attack of pain beneath the right scapula and through the right side of the chest to the right hypochondrium. There was tenderness in the latter region and x-ray examination at that time showed the presence of an enlarged gallbladder containing stones. The patient refused operation and since this time the pain in the shoulders and arms has continued intermittently and is very variable in intensity. She has two varieties of pain: One is situated chiefly in the right hypochondrium and the right axilla radiating through to the right scapula and extending somewhat across the chest anteriorly toward the left; the other pain is the former aching pain felt beneath the left breast radiating when it is severe to the back and to the left arm or to both arms. For the last three or four months she has become unable to walk any distance on account of a sense of oppression in the anterior chest combined with shortness of breath. The abdominal symptoms became worse at that time and she had an attack of diarrhea lasting about one week. She had one attack of severe palpitation associated with a sense of very rapid heart action lasting for three hours and stopping spontaneously. This may have been a paroxysmal tachycardia and has never been repeated. Recently she has had a very severe attack of pain across the lower chest and upper abdomen radiating to the arms. There was no nausea or vomiting. There was no sweating and there was no apparent prostration associated with this attack. The blood pressure did not fall from its usual height during this attack making it unlikely that it was due to coronary thrombosis.

This patient illustrates several varieties of pain which might be confused with the pain resulting from coronary arteriosclerosis, and in addition she has hypertension and some cardiac enlargement which might possibly indicate the presence of coronary arteriosclerosis itself. Throughout this long period of observation her electrocardiogram has remained normal and the outline of the heart by x-ray has not changed in size or shape. The left-sided pain which bothers this patient is probably due to her colitis with resulting tension upon the diaphragmatic attachments of the splenic flexure of the colon; the right-sided pain to the results of cholelithiasis. The severe attacks are probably due to the latter also, but her shortness of breath and sense of pressure in the anterior chest on walking I believe to be due to the weakening effect upon her body of this long-continued chronic illness. It does not seem necessary to diagnose any specific cardiac condition in this case in order to explain the symptoms.

Complicated or atypical cases like the last three noted are a frequent source of confusion to the physician. There has been so much discussion of precordial pain of late that we are now in need of special emphasis and discussion to point out that the heart is not by any means the only cause of pain in this situation. Precordial pain arises quite commonly from other organs and the ones most often so affected are the colon and the stomach. There are other noncardiac diseases which may cause symptoms resembling the angina of effort including such things as mediastinal tumor, tumor of the esophagus, esophagospasm pleural adhesions, especially if these affect the central portion of the diaphragm, cardiospasm, gastric flatulence, colitis, distention of the colon with gas especially if this is marked at the splenic flexure, cholelithiasis with reflex gastric "indigestion," or the gastric or colonic disturbances due to adhesions about an infected gallbladder. Besides these, intercostal neuritis, and the irritation of the dorsal nerve roots due to osteo-arthritis of the adjacent vertebra must be borne in mind. The severe attacks due to coronary thrombosis may be simulated by the onset of lobar pneumonia, or by herpes zoster, by a perforating gastric ulcer or by acute pancreatitis. The emphasis upon the heart so evi-

dent in medical literature during recent years has made for too much "heart consciousness" on the part of the physician as well as on the part of certain patients so that the danger is that you may be induced to think first of the heart when symptoms of this character are complained of rather than to gather in all the details of the history and the physical examination and arrive at a correct diagnosis.



CLINIC OF DR. A. S. BLUMGARTEN

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SPONTANEOUS HYPOGLYCEMIAS IN ENDOCRINOPATHIES

THE object of this presentation is to call attention to several syndromes of spontaneous hypoglycemia which occur in various endocrinopathies. Until recently diabetes was the principal manifestation of abnormal carbohydrate metabolism which was thoroughly studied, although several other forms of glycosuria have long been known. The introduction of insulin as a common therapeutic measure with the frequent development of symptoms of hypoglycemia resulting from excessive dosage of insulin have enabled us to recognize various syndromes of hypoglycemia clinically.

Spontaneous hypoglycemia probably has various etiologic factors both nonendocrine as well as endocrine because carbohydrate metabolism is controlled by the pancreas, the liver, the adrenal, the thyroid, and pituitary glands. We shall therefore discuss the glandular mechanism in the production of hypoglycemia briefly in order to indicate the different types of spontaneous hyperinsulinism and their manifestations.

Pancreas and Carbohydrate Metabolism.—The function of the pancreas in carbohydrate metabolism is so well known that it does not require detailed discussion. Diabetes results when the islands of Langerhans of the pancreas fail to produce sufficient insulin. This may result from a lesion of the pancreas itself or from an indirect influence on the pancreas from irritation at the base of the brain or irritation of the sympathetic nervous system, or from hyperthyroidism. Insulin is a definite specific

for diabetes and essentially its function is to increase the oxidation of glucose in the blood and tissues and to stimulate the formation of glycogen in the liver.

On the other hand, spontaneous hypoglycemia may result from hypersecretion of the islands of Langerhans either from a direct lesion of the pancreas or from indirect factors and probably occurs in various forms according to the mechanism involved. Excessive doses or excessive secretion of insulin causes insulin shock from which the patient recovers slowly if the glycogen content of the liver has been reduced.

Liver and Carbohydrate Metabolism.—The liver is the most important organ in carbohydrate metabolism. It stores the end products of carbohydrates as glycogen and liberates it when required by the muscles and other body tissues. The glucose tolerance test which determines the amount of carbohydrates which the patient can ingest without developing glucose in the urine and the level at which the blood sugar is maintained is really a test of the liver influence on carbohydrate metabolism. However, the storage and liberation of glycogen is controlled by other ductless glands, especially the pancreas, the adrenals, and the thyroid.

The pancreas by means of its insulin stimulates oxidation of liberated glycogen and also increases its formation in the liver. It reduces the glycogen stores of the liver if the patient is well fed, but it does not influence its storage, and in fact it may even retard it during starvation.

The adrenal glands by means of the secretion of epinephrine increase the liberation of glycogen from the liver and stimulates its oxidation.

The thyroid is an important factor in liver function. It increases the mobilization of glycogen from the liver and therefore affects carbohydrate metabolism in association with the secretion of the pancreas and the adrenals.

Adrenals in Carbohydrate Metabolism.—The adrenal glands play an exceedingly important rôle in carbohydrate metabolism. Blum was the first to demonstrate that injections of epinephrine cause hyperglycemia and glycosuria. Its effect is

more lasting if a diuretic is given together with the epinephrine. However, even after the glycogen has totally disappeared from the liver, as in starvation for instance, injections of epinephrine will still raise the blood sugar and produce a glycosuria.

Adrenalin antagonizes the effect of insulin on blood sugar, but both raise the respiratory quotient and act on the inorganic phosphates. The removal of the pancreas is followed by an increased secretion of epinephrine which causes the hyperglycemia and glycosuria.

Removal of the adrenals lowers the blood sugar and the capacity to increase blood sugar response by such experimental methods as piqure of the fourth ventricle is retarded.

Boothby and Rowntree demonstrated that hypersecretion of epinephrine occurs during hypoglycemia in an attempt to overcome the condition. This accounts for the dilated pupils, the sudden rapid heart action, and the spontaneous recovery from hypoglycemia. Experimentally insulin is more fatal in adrenalectomized animals than in normal ones.

Thyroid and Carbohydrate Metabolism.—The thyroid has both a direct and an indirect effect on carbohydrate metabolism. The direct effect is to increase the mobilization of sugar. The indirect effect is through its action on insulin and the adrenals. Thyroid hypersecretion lessens the sensitivity of the patient to insulin at first, followed by hypersensitiveness. Thus an animal which has been on thyroid feeding for some time becomes so insensitive to insulin that a dose ten times greater than that which caused convulsions before the thyroid feeding was started causes no symptoms at all. The increased sensitiveness to insulin which then follows is due to the disappearance of glycogen from the liver. Thus if glucose is given to a rabbit treated with thyroid until it becomes hypersensitive to insulin a transitory rise in blood sugar develops followed by a very rapid fall with the development of symptoms of hypoglycemia. The administration of more glucose may relieve these symptoms temporarily by restoring blood sugar but they soon recur.

The thyroid secretion also increases the effect of adrenalin on blood sugar. Thus the injection of epinephrine in thyroid-fed

animals markedly increased the degree of the resulting hyperglycemia.

Pituitary and Carbohydrate Metabolism.—The pituitary gland has only an indirect effect on carbohydrate metabolism. The removal of the pituitary in an animal causes an immediate rise in blood sugar followed by a gradual fall to normal. It is well known that hypopituitarism is characterized by a delayed sugar tolerance.

According to Burns there is a direct antagonism between pituitrin and insulin. Experimentally, if the pituitary gland is normal the injection of insulin does not produce the convulsions of severe hypoglycemia so readily. If the pituitary is removed, however, hypoglycemic convulsions are produced very readily by injections of insulin.

Injections of pituitrin if given intravenously inhibits the hyperglycemia of epinephrine just as insulin does. When pituitrin is given together with insulin it greatly diminishes if it does not entirely prevent the fall in blood sugar. In other words, a dose of pituitrin which by itself would have no definite effect on blood sugar may nevertheless antagonize entirely the hypoglycemic action of insulin.

Symptoms of Spontaneous Hypoglycemia.—Harris was the first to describe cases of spontaneous hypoglycemia. The essential symptoms are: first, a feeling of nervousness and trembling, and then excessive hunger, a feeling of weakness and an "all gone" feeling. These symptoms are followed by objective signs, such as profuse sweating, pallor and flushing, and sometimes by a change in pulse rate. In children the change in pulse rate is an outstanding feature. In adults the sweating is the outstanding symptom. At the same time the flushings become more severe. The feeling of nervousness increases and becomes a definite anxiety or excitement, or even an emotional upset. Patients have shown a loss of power to perform fine movements. At times there is a feeling of hot and cold. Sometimes vertigo or diplopia develops.

When the blood sugar is very much lowered, marked excitement, emotional instability, sensory and motor aphasia, dys-

arthria, delirium, disorientation, and confusion develop, but seldom convulsions; and in some cases there is stupor or coma. The level of blood sugar at which these symptoms occur varies in each individual. Some become aware of the hypoglycemic symptoms when the blood sugar is between 0.08 and 0.09. Others show no symptoms until a level of 0.04 is reached. A severe reaction may be noted when the blood sugar is 0.06, and a mild reaction when the blood sugar is 0.04. A blood sugar of 0.035 is usually accompanied by unconsciousness.

Since Harris' original description numerous cases of spontaneous hyperinsulinism have been described in the literature, but no attempt has been made to differentiate the types of cases according to etiology and symptomatology and the purpose of this presentation is to indicate these variations and types.

Endocrine Factors in Spontaneous Hypoglycemia.—The foregoing facts indicate that disturbances in the pituitary, the adrenals and the thyroid may be etiologic factors in cases of spontaneous hypoglycemia. However, the specific symptomatology and manifestations of the hyperinsulinism may vary according to these factors because each of these glands plays a somewhat different rôle in carbohydrate metabolism.

The fact that normal or excessive pituitary secretion checks the hypoglycemic effect of insulin strongly suggests a dispituitary mechanism in some forms of spontaneous hypoglycemia, especially in cases with prolonged symptomatology. The fact that hyperglycemia results from excessive epinephrine action would suggest the occurrence of hypoglycemia when the secretion of epinephrine is retarded. The antagonism of epinephrine to insulin suggests a lack of balance between these two secretions as a causative factor. The relationship of thyroid and pancreatic function also suggests that hyperinsulinism may develop in certain forms of hyperthyroidism. The following group of cases in which an endocrine disturbance is associated with the manifestations of spontaneous hypoglycemia will illustrate some of the endocrine mechanisms of hyperinsulinism.

Case I. Pituitary Obesity with Attacks of Hyperinsulinism Caused by Reduction Cures.—S. S., a young woman of nineteen years, came under

observation in April, 1931, complaining chiefly of obesity. She had always been stout. Several months ago she saw a physician for the purpose of reducing her weight. The doctor examined her and did a basal metabolism test. He did not tell her what the rate was, but he put her on thyroid extract. About twelve days after the administration of thyroid extract she lost about $18\frac{1}{2}$ pounds but she became very weak and lost her memory. The condition cleared up in about a week by eating large quantities of carbohydrates. A year ago she saw another physician who put her on a diet and gave her some injections of thyroid for about two months. She didn't lose any weight and he then put her on thyroid extract by mouth and a diet for four months, during which she lost 35 pounds. At the end of this period she again became very weak and lost her memory and remained in a state of stupor but asking constantly for food. She remained in bed for about a week on account of this condition, feeling very weak. She stopped dieting and the thyroid extract and the condition improved. About two weeks ago she had another similar attack while taking thyroid without a diet.

The attacks usually come on spontaneously, they will last for about a week, and she then recovers from them. At the present time she is gaining in weight and her bowels are constipated. The diets prescribed for her were usually diets consisting of vegetables, lean meats, fish, eggs, and gluten bread. She does not develop palpitation of the heart, or nervousness from the thyroid medication and diets and her pulse rate does not change very much. Her mother, who came with the patient, described the attacks as intense weakness with perspiration, a dazed feeling, and the patient remains in a state of stupor or semicoma during that time.

The past history does not reveal anything specific except for the fact that she had whooping cough and measles in childhood.

Menstruation began at eleven years of age, her periods were regular, and she bleeds for five days profusely. She has no symptoms at that time.

The patient is very fond of sweets, she takes an occasional cup of coffee and an occasional cigarette.

The family history reveals the following: Her father is a well-built man, alive and well, and fifty-five years of age. Her mother is of medium stature and inclined to stoutness, and as a child she suffered from headaches. She has a brother of twenty-seven years of age, of medium stature, and another brother of twenty-four years of age who is tall and thin. The patient is the youngest child.

Physical Examination.—The essential positive findings on examination were: Weight, 167 pounds; height, $61\frac{1}{2}$ inches; span, 154.2 cm.; lower extremity, 80 cm.; torso, 74.2 cm.; pulse, 80; blood pressure, 125/80.

A rather stout, dark-complexioned girl. No abnormalities of the skull. Eyes show no abnormalities. Teeth are in good condition. Thyroid was somewhat enlarged, about 25 per cent. Thoracic viscera are normal. Abdominal viscera are normal. Patient shows definite adiposity, confined principally to the lower half of the body.

Laboratory Examinations.—*Basal Metabolism.*—Minus 17 per cent; basal metabolism (after high protein test meal), minus 4 per cent.

Blood Count.—Hemoglobin, 88 per cent; red blood cells, 4,550,000; white blood cells, 11,300; polynuclears, 71 per cent; small lymphocytes, 21 per cent; large lymphocytes, 3 per cent; eosinophils, 1 per cent; basophils, 1 per cent; young cells, 3 per cent; coagulation time, one and three-quarter minutes.

Urinalysis.—Color, amber; appearance, clear; reaction, acid; specific gravity, 1034; albumin, 0; sugar, 0; acetone, 0; microscopical, mucus.

Blood Chemistry.—Icterus index, 6.7; calcium, 10.7; phosphorus, 3.8; uric acid, 2; creatinine, 1; sugar, 0.08; chlorides, 556; urea nitrogen, 19; urea, 39.

Wassermann Test.—Negative.

Sugar Tolerance:

	Blood.	Urine.
On fast	108	0
1 hour after glucose	156	0
2 hours after glucose	113	0
3 hours after glucose	084	0

Subsequent Notes.—On May 30, 1931, after being placed on a high protein low carbohydrate diet of 1000 calories and thyroid extract she began to feel very tired and dizzy and this feeling became so bad that she had to lie down. She remained in a sort of daze, she didn't know whether the people about her were real or whether she was dreaming about them. A blood sugar taken at that time was 0.06. This condition lasted until June 8, 1931. During that time, in spite of her drowsiness, she went back to her occupation as a book-keeper but she could not do any figuring. She had no headaches and she wasn't nervous. This attack was similar to the previous attacks. She attempted to fight off the feeling, but the condition increased to such a point that she had to go to bed. Her mother states that during the attack she was unable to answer questions correctly and she had a constant craving for food, especially candy and cake. As a result of this constant ingestion of candy and cake the condition gradually subsided and she responded well.

Comment.—This patient suffered chiefly from obesity, with evidence of pituitary stigmata. The administration of a low carbohydrate diet or thyroid extract evidently produced a condition of hypoglycemia which was indicated by the symptomatology and the low blood sugar taken during one of the attacks.

The spontaneous hypoglycemia may be explained on the basis of her dyspituitarism and the treatment. The dyspituitarism probably increased her sensitivity to the normal insulin secretion so that consequently when she was placed on a low carbohydrate diet the blood sugar was so reduced either permanently or periodically as to develop hypoglycemia. Furthermore, when thyroid extract was added to the treatment the

sensitivity to insulin secretion was still further increased, with a consequent production of hypoglycemia.

Case II. Spontaneous Hypoglycemia Associated with Adrenal Insufficiency.—V. G., a middle-aged man, of sixty-one years, came under observation in November for an attack of syncope, with loss of consciousness.

He had been perfectly well until about three weeks before the onset of the illness after he had just returned from a day in the country during which he performed a great deal of physical labor which he hadn't done for years. About an hour or two after breakfast, while reading, he suddenly felt himself swooning, he felt that all the blood vessels of the face were congested and he thought he was going to die. He threw himself on the floor, thinking that was the best thing to do, but he kept getting worse. Finally some whisky was given to him, a physician was called, who arrived in about ten minutes, and he at first thought the patient had a heart attack. The pulse was very weak and thready and the patient looked pale and felt cold. During the attack he suffered a great deal with gaseous movements in the abdomen. In a few hours the condition improved, the patient got up from the floor and went to bed, where he remained for about ten days. During that time he had frequent attacks of weakness. A cardiologist was called in and found his heart condition normal and that patient had a low blood pressure ranging from 90 to 60. A possibility of a gastro-intestinal condition was thought of and a gastro-intestinal series of x-rays was taken, which was negative. Following the attack the patient felt miserable and very much depressed for a couple of weeks, largely due to the fact that he thought he was going to die. He had all sorts of examinations made. All the examinations revealed nothing organic.

During the first week of the illness he lost about 6 or 7 pounds in weight and his bowels only moved periodically. He has never been able to take milk or eggs without getting toxic symptoms from them and he can't stand fats. He is an introspective type of person.

The past history revealed the following: Scarlet fever at the age of six years; malaria at the age of twelve; angioneurotic edema and catarrhal jaundice around the age of twenty; frequent attacks of grippe and sinusitis.

He has a great craving for carbohydrates, but in spite of that he doesn't gain much in weight. He smoked heavily until the recent attack and then he stopped it, thinking that it was a causative factor.

The family history was negative.

Physical Examination.—The essential positive findings on examination were: Weight, 145½ pounds; height, 68½ inches; span, 18½ cm.; lower extremity, 89 cm.; torso, 95 cm.; pulse, 76; blood pressure, 105/70.

A rather thin, dark-complexioned, middle-aged man. Skin is smooth, soft, no tache, no Sergeant's line; face becomes flushed during the examination. Eyes are brown in color; pupils react normally to light and accommodation. Teeth are in good condition. Thyroid is palpable, but not enlarged. Abdomen is rather scaphoid, slightly sensitive in the right lower quadrant; kidneys were not palpable.

Laboratory Examinations.—Basal Metabolism.—Minus 18 per cent.

Blood Count.—Hemoglobin, 100 per cent; red blood cells, 4,540,000; white blood cells, 7400; polynuclears, 64 per cent; small lymphocytes, 27 per cent; large lymphocytes, 8 per cent; eosinophils, 1 per cent; young cells, 1 per cent; coagulation time, two and a half minutes.

Urinalysis.—Color, amber; appearance, clear; reaction, acid; specific gravity, 1020; albumin, 0; sugar, 0; acetone, 0; microscopical, a number of calcium oxalate crystals and few bacteria.

Sugar Tolerance:

	Blood.	Urine
On fast.....	100	0
1 hour after glucose.....	163	0
2 hours after glucose.....	143	0
3 hours after glucose.....	078	0

Comment.—This patient showed no evidence of organic disease. The essential findings were a constitutional asthenic make-up, with a low blood sugar, and a low basal metabolic rate of -18 per cent without clinical evidence of hypothyroidism. While the fasting blood sugar was not significant, the sudden drop at the end of the sugar tolerance test was significant. The result of this sugar tolerance test indicates that while the patient may have a normal fasting blood sugar, he burns up his sugar so quickly that he develops a hypoglycemia. In view of the asthenic constitution and the probably constitutional adrenal insufficiency associated with this condition, the attack of syncope was probably due to a hypoglycemic reaction which may be explained on the basis of an insufficient adrenal secretion to neutralize the insulin demand necessary to utilize carbohydrates, especially at the onset when he performed an excessive amount of unusual physical exercise. The administration of glucose and carbohydrates relieved the attacks. He has had several attacks since, which have always been relieved by the administration of carbohydrates.

Case III. Spontaneous Hypoglycemia as a Premenstrual Symptom in a Constitutional Asthenic.—E. E., a young married woman of thirty-three years, came under observation in February, 1932, complaining chiefly of attacks of periodic weakness and exhaustion in the morning which occur with marked intensity for several days before menstruation.

The illness began following an operation seven years previously for the removal of a cystic ovary. Ever since that time she has been developing

attacks of intense exhaustion, a feeling of coldness, tremors, excessive perspiration, and anxiety which usually occurs several days before the onset of menstruation. The patient is sensitive to various proteins, she suffers from hay fever due to ragweed sensitiveness, she has frequent attacks of palpitation and she rarely gains in weight.

As a baby she had a tuberculous lymph node removed; she had several streptococcus infections; at the age of eighteen or nineteen she was operated upon for a cystic ovary and then again before the onset of the present illness; she has a curvature of the spine which never bothers her except when she is in a weakened, rundown condition.

Menstruation began at the age of thirteen, periods were always regular, and she bled for eleven days profusely before she was operated; since the operation she bleeds for seven days profusely. She has intense burning and flushes for several days before menstruation and she gets, in addition, the symptoms indicated in the chief complaint for several days before the onset of menstruation.

She smokes a good deal, takes 1 cup of coffee a day, and she likes her foods well seasoned.

The family history is not significant.

Physical Examination.—The essential positive findings on examination were: Weight, 118½ pounds; height, 65½ inches, span, 169 cm.; lower extremity, 82 cm.; torso, 87 cm.; pulse, 90; blood pressure, 122/78.

A rather thin, dark-complexioned young woman. Skin is smooth, slightly moist, slowly appearing tache, no Sergeant's line. There is considerable pigmentation of the skin. The hair is black in color, fine and brittle. Eyes are blue in color and react normally to light and accommodation. Teeth are in fairly good condition. Thyroid is palpable and enlarged about 20 per cent. She has a very definite scoliosis of the spine, with marked convexity in the right lumbar region and a convexity with rotation in the lumbo-sacral region. The thoracic viscera were normal. There is tenderness in the lower part of the abdomen. Extremities showed no abnormalities.

Laboratory Examinations.—*Basal Metabolism.*—Minus 2 per cent.

Blood Count.—Hemoglobin, 78 per cent; red blood cells, 3,830,000; white blood cells, 10,800; polynuclears, 58 per cent; small lymphocytes, 24 per cent; large lymphocytes, 3 per cent; eosinophils, 3 per cent; basophils, 5 per cent; coagulation time, two and one-quarter minutes.

Urinalysis.—Color, amber; appearance, clear; reaction, acid; specific gravity, 1025; albumin, 0; sugar, 0; acetone, 0. Microscopical: Mucus and a few epithelial cells.

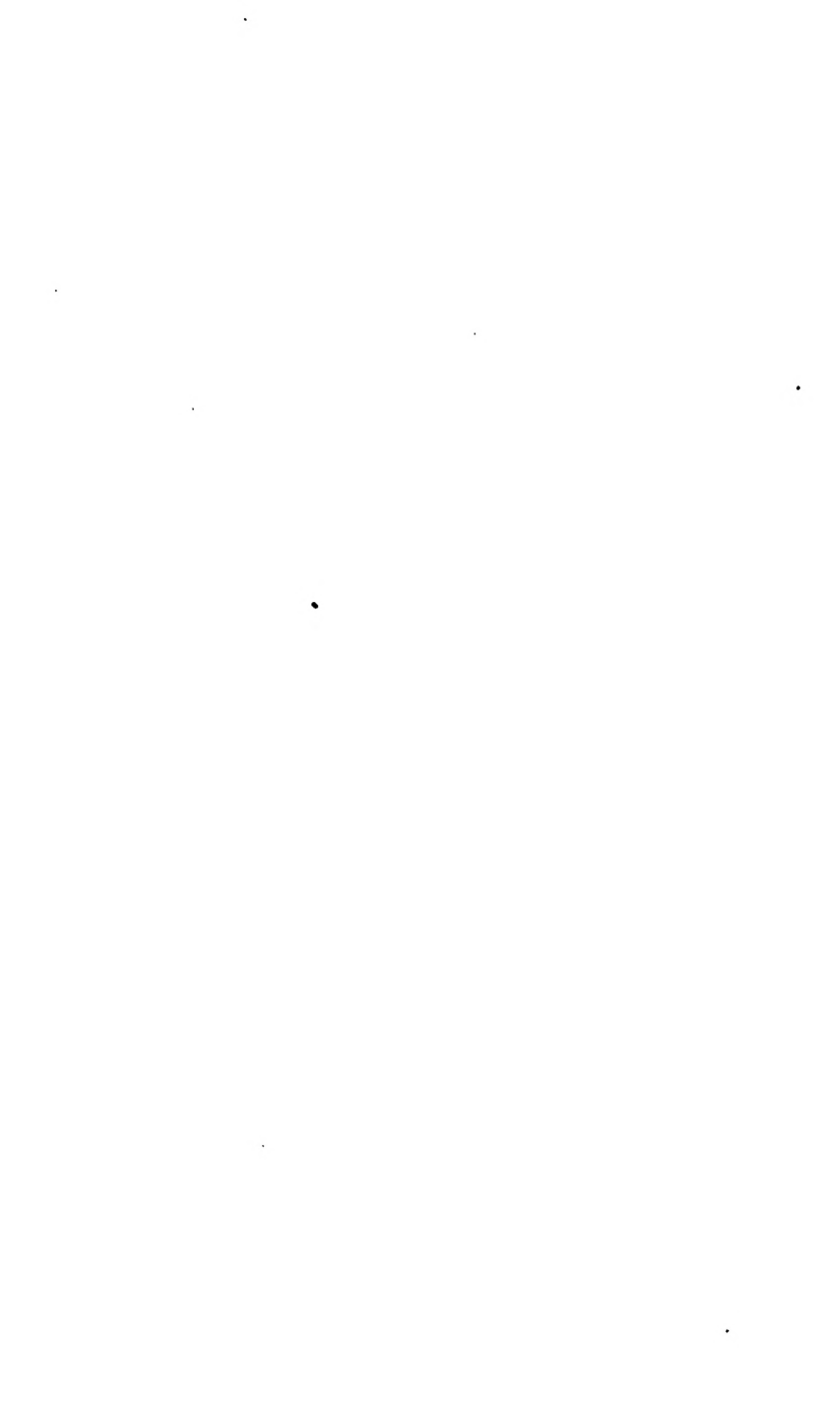
Blood Chemistry.—Icterus index, 5; calcium, 11.0; phosphorus, 2.7; cholesterol, 133; uric acid, 4.7; sugar, 0.091; creatinine, 1.2; chlorides, 514; urea nitrogen, 11; urea, 23.

Sugar Tolerance:

	Blood.	Urine
On fast	108	0
1 hour after glucose	166	0
2 hours after glucose	129	0
3 hours after glucose	092	0

Comment.—The patient is a constitutional asthenic with definite evidence of dysfunction of the autonomic nervous system. The blood sugar figure between the attacks was not at all significant, but during the attacks the blood sugars on two occasions were 0.08 and 0.065 respectively. The patient, however, suffered with the usual asthenic symptoms between menstrual periods. The explanation which may be given for the symptoms which develop before menstruation is that the imbalance of the autonomic nervous system which occurred as a premenstrual system is associated with an insufficient adrenal secretion eliminating the normal check on insulin secretion with the production of hyperinsulinism. The patient usually obtained prompt relief by the administration of carbohydrates or sugars in some form.

Summary.—Spontaneous hypoglycemia is a frequent condition associated with various endocrinopathies. Dyspituitarism, adrenal insufficiency, and frequently hyperthyroidism may act as factors in the production of spontaneous hypoglycemia. Three cases of spontaneous hypoglycemia are presented: (1) A case of hypoglycemia developing from a low carbohydrate diet in a case of dyspituitarism and the development of the symptomatology from the administration of thyroid; (2) a case of spontaneous hypoglycemia resulting from insufficient adrenal secretion thereby eliminating the check on insulin secretion; and (3) a case of spontaneous hypoglycemia developing as a premenstrual symptom in a constitutional asthenic with probable evidence of adrenal insufficiency.



CLINIC OF DRS. MILLS STURTEVANT AND IRVING GRAEF

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HENOCCH-SCHÖNLEIN PURPURA WITH PARALYTIC ILEUS AND RHEUMATIC CARDITIS

THE etiology of Henoch's purpura has run the gamut of speculation. Variousl^y ascribed^{1, 2} to toxins, bacteria, food sensitization and as the visceral phenomena in idiopathic purpura, it is our purpose here to discuss a case exhibiting the characteristic visceral lesion in association with active rheumatic carditis.

The patient was an Irish bellboy, twenty-six years old, who was admitted to the wards of the Third (New York University) Medical Division at Bellevue Hospital on April 13, 1932. He gave no history of any chronic or hereditary disease in his family. His father, mother, three brothers and three sisters were living and well. He said he had had rheumatism when twenty-four years of age (1930). Active symptoms had lasted three days and were not treated. There was no history of venereal disease, or any other disease whatsoever. He was an occasional user of alcohol. He smoked about ten cigarettes a day.

His present illness began about two weeks before admission when he had caught cold, beginning with a chill followed by fever. He developed productive cough and a diffuse greenish expectoration; a physician diagnosed grippe. He became constipated and lost his appetite. Five days before admission he began to have abdominal pain which was generalized. At the same time constipation became so marked that in the two weeks of his illness he had had only two movements. He lost about 7 pounds of weight. He "guessed" that he had vomited five times in the week prior to admission. The vomitus was greenish and did not contain blood. He had not seen blood in his stools. He had seen "blood" in his urine the day prior to admission. On examination he seemed to be a well-developed white male, lying quietly in bed. There was no dyspnea, no orthopnea, no cyanosis. His tongue was

dry. The pupils were equal and reacted to light and accommodation. Lungs were clear. The apical impulse of the heart was within the midclavicular line in the fifth intercostal space. Rhythm was regular, rate 84, no thrills or murmurs.

Examination of the abdomen showed marked distention. There was tenderness on the right side particularly in the right lower quadrant where skin hyperesthesia could be demonstrated and definite, though slight, rebound tenderness. There was no clubbing of the fingers, no edema, no eruption. There were no purpuric lesions of the visible mucous membranes. Neurological examination was negative.

It was thought that there was abdominal inflammation, probably appendicitis or intestinal obstruction. On the following day the patient appeared worse. Bowels had not moved, did not respond to enemata or irrigation. Vomiting increased. There was marked tenderness in both lower quadrants and on rectal examination, lateral pressure elicited tenderness. Peritonitis seemed certain.

Leukocytes numbered 14,200; polymorphonuclear leukocytes, 82 per cent; lymphocytes, 18 per cent; hemoglobin (Dare), 82 per cent; red blood cells, 4,340,000. Urine, acid; specific gravity, 1020; 2 to 3 plus albumin; 2 coarsely granular casts with 3 white blood cells to each high power field. Operation seemed indicated and was performed on the same day by Dr. T. Galvin.

Operative findings were as follows: The lower end of the ileum and mesentery appeared hemorrhagic and there were numerous areas of subserosal ecchymoses. The peritoneal cavity contained a small amount of soapy-like exudate. The spleen was small. The mesenteric lymph nodes were enlarged. The gut throughout was empty and distended. The appendix was small and sclerotic, otherwise normal.

The patient did poorly after the operation. The distention increased. Intestinal irrigation yielded no blood in the feces. Within forty-eight hours the temperature rose from 101.6 F. to 105.6 F. The pulse ranged between 130 and 150.

Leukocyte counts done on the 14th and 15th respectively revealed 8550 and 6600 leukocytes. Differential smear showed 74 per cent polymorphonuclear leukocytes, 3 transitional cells; 18 lymphocytes, and 5 meta II's. No abnormal cells were seen in the smear. No reference was made to platelets.

A Widal test was done and yielded agglutination in dilutions of 1 to 40 for *Bacillus typhosus* and paratyphoid A and B. On this day ecchymotic spots appeared over the elbows and back and allergic purpura was diagnosed. Delirium appeared and the patient died during the night of April 16th in an extremely toxic state. There was no swelling of the joints at any time.

Postmortem examination, limited to an abdominal incision, revealed the following significant findings:

There was no evidence of scars, no superficial adenopathy or clubbing of the fingers. On the medial and lateral aspects of the knees, on the dorsal aspect of the left forearm, and on both sides of the neck, there were confluent and discrete areas of intracutaneous and subcutaneous purpuric lesions, no vesiculation.

The peritoneal cavity contained 50 cc. of light brown turbid fluid. The peritoneum itself was smooth and shining. The coils of the small intestine were markedly distended and the walls were extremely thin. There were visible numerous areas of hemorrhage in the distal half of the ileum. The abdominal organs were natural in position and relationship. The pleural and pericardial cavities contained a small amount of clear fluid.

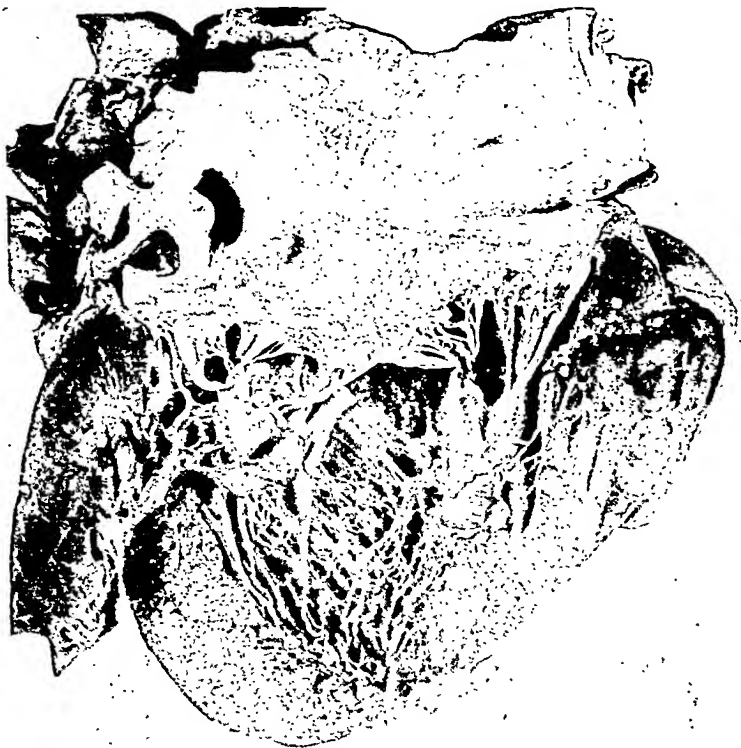


Fig. 25.—Photograph of the open heart showing a somewhat thickened mitral valve diffuse connective tissue and somewhat hypertrophied papillary muscles. There was no stenosis. Close inspection reveals an irregular row of verrucae at the line of closure. These are best seen on the anterior leaflet.

Heart.—The heart appeared of normal size, weighing 280 Gm. There was a normal amount of subepicardial fat and 4 or 5 "milk patches." The pericardium was smooth and shining throughout. On section the chambers were filled with "chicken-fat" clot. They appeared normal in size. The aortic, pulmonic, and tricuspid valves appeared natural. The mitral orifice was natural (Fig. 25). Inspection of the cusps of the mitral valve revealed a row of firm, grayish-yellow verrucae along the line of closure and raised some

3 mm. above the surface. Delicate blood vessels could be seen in the substance of the leaflets and extending to the free margin. The chordae tendineae appeared somewhat thickened, grayish white, but not shortened. The endocardium was smooth and shining throughout. The myocardium throughout

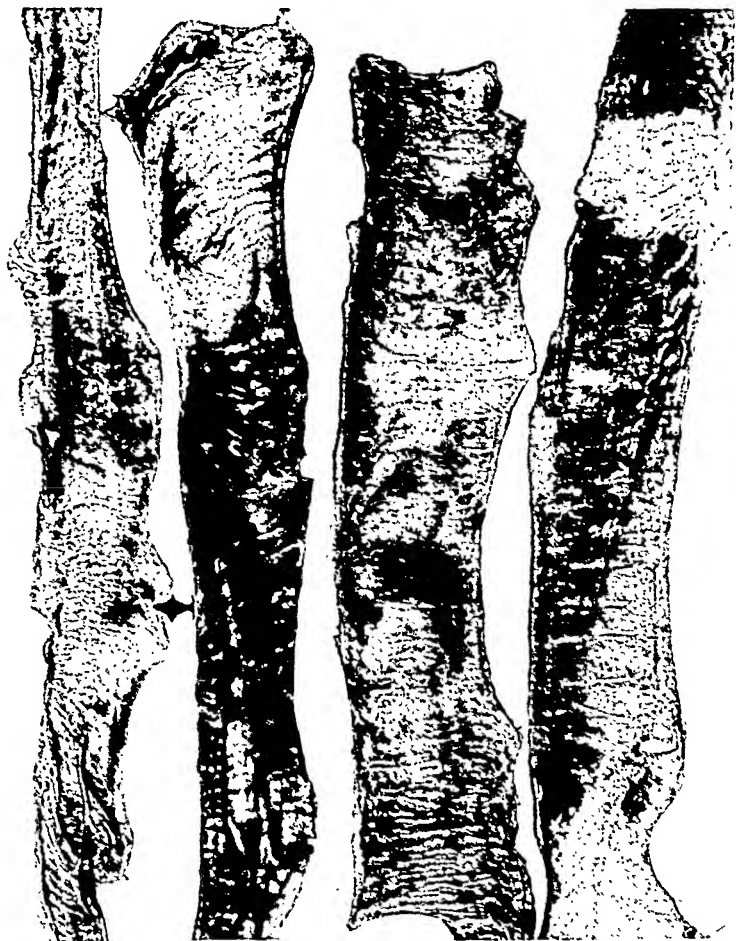


Fig. 26.—Photograph of portions of the ileum showing discrete and diffuse submucosal hemorrhages. These appear black in this photograph. The arrow points to the only ulcer found.

showed no changes. The mouths of the coronary arteries were natural. On section, the branches of the coronary arteries revealed no naked eye changes. The aorta was of normal caliber and free from atheroma.

Lungs.—Were normal in size. The visceral pleura was smooth and shin-

ing. The lungs were crepitant throughout. They showed no areas of consolidation. On cut sections, there was evident congestion or hemorrhage at the base. The trachea and bronchi were natural. The larger branches of the pulmonary artery showed no changes.

Liver.—The liver was slightly enlarged, weighing 1350 Gm. The capsule was smooth and translucent. On section the characteristic markings of chronic passive congestion was seen. There were no other changes. The gallbladder and biliary passages were natural.

Spleen.—The spleen weighs 165 Gm. Its capsule was smooth, slate-gray; on section, the pulp was firm and deep red in color. The trabeculations were prominent. The follicles were not seen.



Fig. 27.—Low power microphotograph of a section of the myocardium showing the remnants of an Aschoff body and perivascular fibrosis adjacent to a small branch of the coronary artery.

Gastro-intestinal Tract.—The esophagus was natural. The stomach was normal in size and contained about 200 cc. of light brown fluid. The duodenum was natural. In the jejunum there were several small, irregularly distributed areas of interstitial hemorrhage beneath the mucosa, best seen from the serosal aspect. There was no peritoneal reaction over these areas. In the ileum (Fig. 26) there were many more of these hemorrhages, several diffuse coalescent ones measuring 10 cm. in length. Close inspection of the peritoneum and mucosa over these areas revealed no notable naked eye changes. One small ulcer was found about 5 mm. in diameter 35 cm. from the ileocecal valve. There were no other areas of ulceration. The small

intestine throughout was markedly dilated and the wall thinned out. The contents were liquid and yellow in color. The appendix and large intestine were normal except for a moderate amount of congestion. The mesentery was congested and contained several moderately enlarged lymph nodes. The rectum was natural.

The examination of the pancreas, adrenals, kidneys, bladder, prostate, and testes revealed no notable naked eye changes.

Microscopical Examination.—Heart and Great Vessels.—Numerous sections of the myocardium and the valve leaflets were taken. Aschoff bodies were found with ease in sections of the mitral valve including the myocardium of the posterior wall (Fig. 27), of the right auricle (Fig. 28), and of both



Fig. 28.—Low power microphotograph of a section from the right auricle showing the spindle-shaped Aschoff bodies adjacent to a larger branch of the right coronary artery. Note the absence of necrosis or giant cells.

papillary muscles of the left ventricle. They were distinctive because of their spindle shape. Areas of necrosis were absent and none of the bodies studied showed giant cells. The section of the mitral valve (Figs. 29, 30), including the verrucous vegetation described grossly, showed well-developed characteristic verrucae consisting of fibrin thrombus undergoing organization and resting upon a base composed of proliferated histiocytes and leukocytes.

The base extended well into the valve and study of the proximal portion of the valve revealed interstitial inflammatory changes as well as new and old blood vessels. In some sections of the myocardium patchy scars were seen

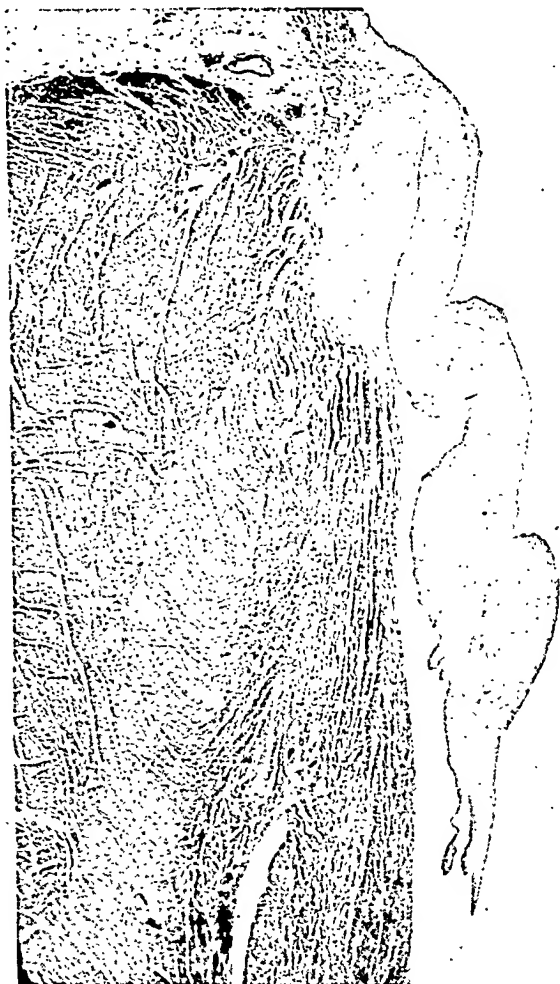


Fig. 29.—Microphotograph ($\times 8$) of a section of the posterior leaflet of the mitral valve showing the slightly thickened, though not shortened, leaflet and the verrucae at the line of closure. Note the absence of scarring at the ring.

around the blood vessels and extending into and interrupting the muscle bundles. Sections of the aorta and pulmonary artery revealed no striking changes. Examination of the coronary arteries revealed an occasional area of intimal

hyperplasia which was usually sharply delimited and barely extended into the lumina of the affected vessels.

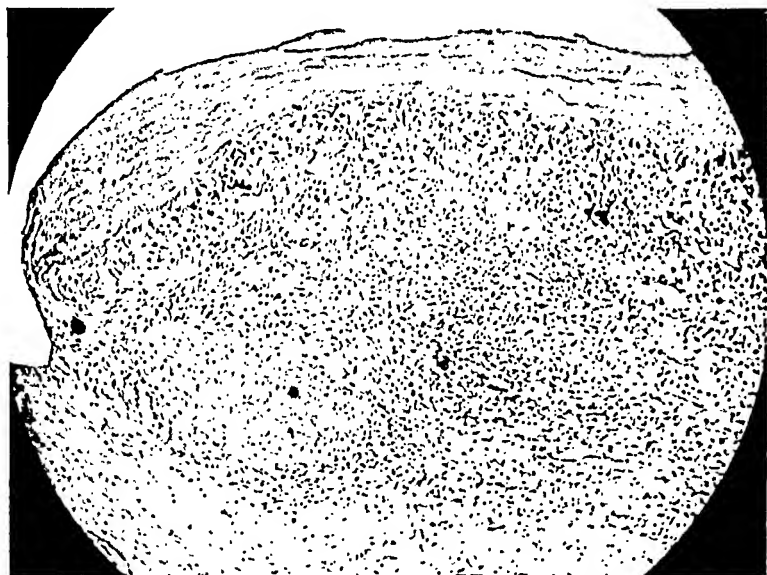


Fig. 30.—Low power microphotograph of the verrucae seen in Fig. 29 showing the thrombotic deposit on the surface and the remnants of a palisade arrangement of the proliferated histiocytes, as well as infiltration by leukocytes and early formation of new blood vessels.

Intestines.—Numerous sections were taken of the wall of the small intestine, the branches of the superior mesenteric artery, the mesenteric attachment of the intestine, and the mesenteric lymph nodes. In none of these was



Fig. 31.—Microphotograph ($\times 5$) of a section of the ileum showing the location of the hemorrhage.

an inflammatory lesion found. The hemorrhages described grossly were located in the submucosa and were associated invariably with intensely congested veins (Figs. 31, 32). The hyperemia of the veins and the relative is-

chemia of the arterial branches were conspicuous. There was desquamation and autolysis of the surface epithelium and glands. Sections which included a Peyer's patch disclosed no change other than hyperemia.

Lungs.—Sections of the lungs showed focal areas of intra-alveolar hemorrhage and diffuse pulmonary edema.

Liver.—Section of the liver confirmed the gross diagnosis of chronic passive congestion. There was dilatation of the central veins and sinusoids with atrophy of the adjacent parenchymatous chords.

Sections of the other organs confirmed the gross diagnosis.



Fig. 32.—Low power microphotograph of a section of the ileum showing superficial autolysis of the mucosa and erythrocytes in the submucosa.

Final Pathologic Diagnosis.—Heart: Verrucous endocarditis of the mitral valve; chronic rheumatic myocarditis. Lungs: Congestion, focal pulmonary hemorrhage. Liver: Chronic passive congestion. Kidneys: Congestion. Gastro-intestinal tract: Focal and diffuse interstitial hemorrhages of the small intestine; solitary ulcer of the ileum; congestion of the mesenteric lymph nodes. General: Purpuric hemorrhages of the extremities; operative incision, right lower quadrant.

Comment.—The case presents several interesting points for

discussion. In attempting to explain this patient's disease we have little to choose from. Manifestly his symptoms followed an acute upper respiratory infection and manifestly they were accompanied by characteristic endocardial changes and evidence of rheumatic myocarditis. While the myocardial lesions appear old the endocardial lesions exhibit characteristics seen in transition from the acute to subacute stages and, while their exact age cannot be determined, it is reasonable to assign their origin to the disease of the last three weeks.

The absence of specific vascular changes in the many blocks of the mesentery and intestinal wall studied leaves us with the assumption that the ecchymoses were due to altered capillary permeability, while the findings in the valves and myocardium attest to the existence of a rheumatic infection.

The absence of gross intestinal hemorrhage is explained by the location of the ecchymoses in the submucosa. Since there was evidence of chronic passive congestion in the liver, stasis may have added to the factors producing the extravasations. Paralytic ileus appears to have been the chief factor in the production of symptoms and in the cause of death.

Because of the frequent association of urticaria and arthritis with purpura, recent writers have usually referred to these variable clinical syndromes as allergic purpura (purpura anaphylactoides). Reports are available of cases associated with food sensitization,^{3, 4} bacterial infection,^{5, 6} as a complication of scarlet fever,⁷ and as a sequela of acute tonsillitis.

The mode of the development of the allergic state in the various conditions reported may or may not be operating in this case. Since the existence of allergy in rheumatic fever is generally acknowledge, it seems reasonable to relate the purpuric manifestations in this case to the underlying rheumatic infection.

The mode of death deserves comment. Unfortunately the necropsy was limited to the trunk and we cannot report on the condition of the brain. Purpuric lesions in the brain have been reported¹ and they may have occurred in our patient---certainly they must be thought of when one considers the fulminating course, high fever, and delirium with rapid exodus.

The appearance of the skin lesions after the onset of abdominal symptoms is unusual but not unknown. The absence of splenomegaly is in accord with observations generally recorded.^{1, 2}

In considering an allergic basis for the lesions in our case it is interesting to note the time interval between the onset of the acute upper respiratory infection and the appearance of visceral disease. This recalls to mind the recent work of Poynton and Schlesinger⁹ in which he stressed the latent period seen so often in acute rheumatic fever—namely, between the onset of acute upper respiratory infections and that of visceral symptoms. This might be construed as additional evidence in support of the acquisition of an allergic state and the cases described following tonsillitis and complicating scarlet fever should be considered in the same light.

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S.M.S. MEDICAL COLLEGE
JALPUR.
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DELIRIUM IN PNEUMONIA: ITS TREATMENT WITH ETHOBROME (AVERTIN)

ON December 12, 1932, a colored man was admitted to my service at Harlem Hospital on the third day of his illness which had commenced with sharp pain in the right chest followed by dyspnea, chills and sweats, and a blood-streaked sputum. He was brought to the hospital in pulmonary edema, with dulness and diminished voice and breath sounds over the right lower chest. Because of the many bubbling râles the heart sounds were poorly heard. There was cyanosis and distention, and there had been vomiting. He seemed apathetic.

On admission the temperature was 105.8 F., pulse 126, and respirations 48. Blood pressure, 100/70. White blood cell count, 6800; polymorphonuclears, 5304. A blood culture taken at 8.55 p. m. contained 116 colonies and 88 colonies on each of two agar pour plates.

The patient was given, at first, oxygen by nasal inhaler, then 100 cc. glucose, 50 per cent, followed by insulin (20 units), and chloral hydrate, 15 grains, and bromides, 30 grains. At 9 o'clock 4 cc. of Type I and Type II serum was administered without apparent reaction. The temperature fell to 105 F. at midnight though the pulse was 130. At this time, because the dyspnea and cyanosis were unrelieved, he was placed in an oxygen tent. His pulmonary edema seemed less. At 2 a. m. he was resting quietly though his pulse was very small. At 2.30 he was given another dose of serum.

Suddenly and without any warning, at 4.30 a. m., he became violent and attempted to get out of bed; when restrained, he endeavored to bite the nurse and the orderly. He became more and more terrified and panic stricken, threatening to strike those about him. His excitement increased, and efforts to calm him were futile. He struggled more and more. Suddenly he gasped and collapsed, and in a few moments both pulse and respiration ceased. The whole period of wild excitement had lasted approximately five minutes.

At autopsy the next day, consolidation of the mesial portion of the right lower lobe was found, with a fibrinous exudate and a moderate effusion at the right base. The lower and middle lobes were matted together. Elsewhere the lungs were congested. The heart had stopped in diastole. (Dr. S. Weintraub, pathologist.)

This tragic instance is narrated as an introduction to a discussion of the importance of delirium in pneumonia. Delirium in the course of pneumonia is evidence of grave illness. Of itself the delirium adds much to the cares and responsibilities of the physician and nurse. Without apparent warning, at any time during the disease delirium may set in; it occasionally appears even when the temperature has fallen. Usually, however, the onset of active delirium is heralded by sleeplessness and nervous irritability, anxiety, muscle twitchings or apparent apathy.

When the warnings of oncoming delirium are unheeded or slight, patients may leave their beds and attempt to pursue their regular or new occupations, or seek to attack or escape imaginary enemies or to avoid hallucinatory calamities. They become dangerous to others and are a menace to themselves because they may wander, scantily or unclad, into the cold, and fall or jump from windows. Patients have been brought in naked from adjoining parks, where they have wandered from tenement houses in the small hours of the morning when wife or nurse dozed.

Nurses should always be warned of the possibility of delirium and they should be frequently cautioned, lest the patient be left unwatched for a single moment. If the nurse must leave for supplies, she should be relieved by someone capable of guarding the patient and giving the alarm at the first sign that he is about to leave his bed. The nurse's station should be between bed and window, and if there is the slightest suspicion of delirium, sideboards or blankets should be so placed as to form an impediment to ready access to the floor. The lower sash of windows should be wedged or nailed so that it cannot be lifted. Shatterless glass, small window panes or metal air deflectors should be used in pneumonia wards or hospital rooms for pneumonia patients so as to impede the patient's escape if he attempts to go through the glass, which he may either fail to perceive or believe leads into some other room, or which he may deliberately break as a means of readier escape from a confinement, which to him seems intolerable.

Delirious patients, when opposed, exert themselves to the limit of their strength and become exhausted in the effort to pursue their delirious purpose. If restrained they may exercise great cunning in escaping the restraints or, in attempting to tear the restraint away, tire themselves, frequently bruising the skin of wrists and ankles with violent efforts to undo padded thongs which they believe are nets or the hands of policemen or guards.

On some occasions, when the physicians and nurses humor the patient and apparently enter into and believe the content of his delirium, he is controlled and persuaded to remain in bed but on no account should a delirious patient be trusted, because in order to escape surveillance, he may in turn attempt to delude the nurse into the belief that he is normal and cooperative.

In many cases delirium may be prevented by timely employment of sedatives, especially when patients are sleepless. Pneumonia patients who do not sleep for several nights have been by that fact greatly handicapped, and often die. In the treatment of insomnia of mild or moderate grade, we have employed in alternate cases for a year at a time, at different times, these various sedatives orally, intravenously, and intramuscularly: amytal, morphine, codeine, chloral, chloral and bromides, and dial.

Anoxia, distention, and bacteremia are associated and possibly causally related phenomena which seem to interfere with the ordinarily expected action of the drugs because when these conditions are properly treated sedatives are more efficacious, and when they cannot be completely relieved, the delirium must be controlled by some means or the patients usually die.

It is the treatment of the more severe active types of delirium which is to be considered here—the violent, hallucinating patients who attempt to leave their beds. Formerly we treated these patients with wet packs, or with paraldehyde either by mouth, by rectum or intravenously, but with indifferent results. Subhypnotic doses of sedatives frequently cause excitement and aggravate the condition. Excessive doses may result in such de-

pression of respiration that secretions are retained in the lungs, with cyanosis and ineffective shallow breathing.

In our experience in an effort to give a proper dose of sedative, we frequently fell short of the adequate, or doses which produced an effect were frequently accompanied by such profound narcosis and depression of reflexes that the patients rarely survived.

Small doses of morphine seem to stimulate rather than to depress the cerebrum, and the summation of small doses often unduly depresses the respiratory center. On this account, when Dr. Harvey Cushing narrated his experiments on the effect of ephedrine in cutting short the effect of tribromethanol—ethobrom (avertin)—anesthesia when the drug was brought in contact with the nuclei at the base of the brain, it seemed important evidence that the effect of the ethobrome was largely on the basal nuclei. It then occurred to us that ethobrome would be especially useful, on this account, in anesthetizing those basal nerve cells and blocking out impulses to an already exhausted and therefore probably abnormally reacting cortex. With this in view, we have adopted the use of ethobrome in the control of the deliria of pneumonia, with extremely gratifying results.

Patients frequently sleep for many hours immediately or after a latent period of one-half hour after the rectal administration of ethobrome, without very marked depression of the respiratory center, and awaken refreshed and with normal psychological reactions. The dose given is always less than the recommended anesthetic dose. At first a dose of 50 mg. per kilo of body weight was employed; if this dose was inefficient a dose of one quarter the anesthetic dose was added, making a total of 75 mg. per kilo. Occasionally and rarely it was necessary to repeat the second dose. At the present time we employ 60 mg. per kilo as the initial dose. This is preceded by an enema.

At times the patients are violent and they reject all or a portion of the drug. In such cases we have found it useful to give, intravenously or intramuscularly, a sedative dose of one of the barbituric acid compounds. For this purpose we are now using diallylmalonylurea, known as dial, with urethane, in the dose

0.005 Gm. per kilo, intravenously. Very often at the present time, if the 60 mg. dose of ethobrome is insufficient and reduces the patients from their wild delirium to a low muttering state, dial may be given to induce deeper sleep.

A considerable number of cases have been treated since November, 1931. A full report of our experience is in preparation. Several examples are given in the following cases.

F. B., an acutely ill, adult colored male, aged thirty-nine years, was admitted on the fifth day of his illness (December, 1932) with dyspnea, cough, and pain in his chest. Physical examination revealed consolidation of the right lower and right middle lobes. Admission temperature was 103.4 F., pulse 140, and respirations 38.

At 9.15 P. M., 1 grain codeine was given and at 9.45 P. M. the patient was sleeping. At 5.00 A. M. he again began to cough, had delusions of persecution, and wanted to leave the hospital. He was not noisy, however, and did not attempt to leave his bed, to which side boards were applied. He perspired profusely. With the exception of being talkative at intervals, he was quiet all day, but at 4.00 P. M. attempted to get out of bed. Restraints were applied. Gradually he became more noisy and irrational and sought to remove the restraints. At 3.40 A. M., ethobrome, 4.8 cc., was given. This did not produce a sound sleep but there was less delirium.

During the seventh day the patient was sleepless, noisy and talkative. His temperature was 102.6 F., pulse 108, and respirations 44. At 1.50 P. M., dial, 0.4 Gm., was administered intravenously; apparently there was an immediate effect. He became drowsy, and was quiet until 3.00 P. M. His temperature rose to 104 F. and he was again restless, noisy and talkative. At 10.40 P. M., ethobrome, 4.3 cc., was given; five minutes later the patient was sleeping. On the following morning, when aroused, he was generally improved but still drowsy, and he returned to sleep. His temperature was 102.2 F.

On the eighth and ninth days the improvement continued, his temperature and pulse rate dropped and the signs of delirium disappeared.

T. R., a moderately ill, colored male aged forty-three, was admitted on the third day of his illness with slight cyanosis but without dyspnea. Physical examination revealed a consolidation of the left upper lobe.

Admission temperature was 103 F., pulse 128, and respirations 40. Pneumococcus Type VI was isolated from sputum and lung juice. The blood culture was positive, with 23 and 26 colonies per cubic centimeter on each blood agar plate. Type VI antipneumococcic serum was administered. Subsequent blood cultures were sterile.

Late on the sixth day the temperature was 100 F., pulse 100, and respirations 30. The patient became restless and noisy, and restraints were applied. After an enema at 11.45 P. M., ethobrome, 3.8 cc., was given at 12.15 A. M. The patient was in a muttering delirium. At 1.40 A. M. dial, 0.0144 Gm., was given intravenously, and he slept before the needle was re-

moved from his vein. He awoke at 3.15 A. M. and was restless and irrational. This condition persisted throughout the early morning and at 10.30 A. M., dial, 0.34 Gm., was given intravenously. The patient remained talkative and delirious until 6.00 P. M., when he became drowsy. He rested though he was still talkative when disturbed. He dozed at frequent intervals until 9.00 P. M., when he fell asleep and did not awaken until morning. He was then much improved but still irrational. He was quiet, however, resting during the day, and he became rational towards evening. His condition then improved rapidly.

F. S., a slightly ill, white male aged thirty-seven, was admitted on the fifth day of his illness with an alcohol odor to his breath and with slight dyspnea and marked cyanosis. Physical examination revealed consolidation of the left lower lobe. Admission temperature was 103.6 F., pulse 120, and respirations 30.

On the eighth day, at 9.00 P. M., he was restless and began to talk at random. He was given 1/7 grain morphine. At 1.45 A. M. he attempted to leave his bed and restraints were applied. He remained awake until morning. On the ninth day he was restless, irrational, disoriented and delirious. One ounce of whisky was administered every four hours for 4 doses. He remained restless and had to be restrained at 5.15 P. M. At 10 P. M. he was given 1/6 grain morphine and 1/200 grain scopolamine. He was restless and irrational until 1.00 A. M. when he fell asleep.

The following day he was irrational, talkative, delirious and disoriented. At 9.15 P. M. he was given $\frac{1}{4}$ grain morphine without apparent effect. At 3.00 A. M. he was very irrational and, after an enema, was given, by rectum, 4.3 cc. ethobromic (50 mg. per kilo of body weight which was estimated to be 189 pounds). He fell asleep. He was quiet during the eleventh day, sleeping the greater part of the time. When he awoke he was rational. His condition rapidly improved.

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EPIDEMIC CEREBROSPINAL MENINGITIS IN CHILDREN A CRITICAL REVIEW OF FORTY-FOUR CASES

Definition.—Epidemic cerebrospinal meningitis is an acute infectious disease caused by a specific organism; characterized by inflammation of the cerebrospinal meninges and occurring in epidemic or endemic form.

History.—The first outbreak of cerebrospinal meningitis was reported by Vieusseux in 1805, in Geneva, Switzerland; and subsequently in 1806, in Massachusetts, by Danielson and Mann. Since that time numerous epidemics, of greater or less severity, have been experienced both abroad and in the United States. One of the most extensive outbreaks on record prevailed in New York from 1904 to 1905, in which 6755 cases were reported, with 3455 deaths. The epidemic which occurred in Belfast in 1908, although it claimed fewer victims, had an even greater mortality; it having reached approximately 75 per cent. More recently, outbreaks have visited the United States in 1912, in 1917 and 1918, and in 1928.

Etiology.—*The Organism.*—The causative organism was isolated and described by Weichselbaum in 1887, and designated as the *Diplococcus intracellularis meningitidis*; it is now frequently referred to as the diplococcus which bears his name, also as the meningococcus. It is a gram-negative, intracellular organism, usually seen within the leukocyte. It occurs either in large or small numbers, frequently in pairs or tetrads. According to Gordon, Neal, and others, there are many different strains of the meningococcus, these being distinguishable by their immuno-

logical reactions. In general, however, four main types of the organism are recognized—Types I, II, III, and IV. It has been ascertained that 75 to 80 per cent of the cases of epidemic cerebrospinal meningitis have been caused by Types I and II (usually involving the meninges), and that Types III and IV are more likely to cause septicemia.

The organism is found chiefly in the meningeal exudate, in the cerebrospinal fluid and, less frequently, in the blood, lungs or other organs. The presence of meningococci in the nasal pharynx of patients, during an attack of meningitis, has been noted by Kiefer, by von Lingelsheim, by Councilman, Mallory and Wright, and by others. Included among these are Goodwin and von Sholly, who, during the epidemic of 1905, isolated them from this region in 60 per cent of their patients; and Flack and Andrewes, who, in 1917, recovered them in the majority of their cases.

Mode of Transmission.—Notwithstanding the frequent finding of meningococci in the nasal pharynx of patients during an attack, it is generally agreed that the disease is not easily transmitted by direct contact. This theory seems to be substantiated by the fact that we have never observed the development of a case in the hospital wards in which subjects of the disease were under treatment. There seems little doubt that the condition is disseminated by carriers.

The micro-organism was found by Kutscher in the mucous membrane of 75 per cent, and by Goodwin and von Sholly in 10 per cent of persons who had come in contact with patients. Meningococci have also been observed in the rhinopharyngeal secretion of individuals not known to have been in close proximity with persons suffering with the disease, the likelihood being that the organism was, in turn, transmitted to them by a carrier. Thus an endless chain of carriers is established, capable of spreading the disease in all directions.

Season and Climate.—The majority of epidemics of cerebrospinal meningitis occur during the winter and early spring, the organism seems to have a predilection for temperate climates.

Age and Sex.—It is principally a disease of early life, fre-

quently occurring in infants under one year of age; the second year of life claims the greatest number of victims. Persons over thirty years of age are attacked more rarely, although the condition has frequently prevailed among the soldiers at camp, during various wars. The influence of sex seems negligible.

Hygienic Surroundings.—While the disease is most prevalent in overcrowded districts where unsanitary conditions prevail it is a noteworthy fact that not more than 2 or 3 cases usually occur in one house. The general state of health of the subject and the fact that he has previously experienced other diseases, may act as predisposing factors. Overexertion, trauma to the head and exposure to heat are considered contributing causes. As far as is known, one attack does not seem to confer immunity.

Pathology.—*Macroscopical Lesions.*—Brain and Cord: Patients who die within twenty-four to forty-eight hours show little macroscopical pathology, although an intense hyperemia of all the meninges of the brain and cord is usually found. There is little exudation present early in the disease. Councilman, Mallory, and Wright report that the meninges of the entire brain are equally affected, the process being more pronounced on the lateral surfaces of the convexity, the parietal, and occipital lobes; the meninges over the cerebellum are always involved.

Pathologic findings of a different nature are demonstrable as the disease advances. Exudation gradually increases in amount. It is first seropurulent; later purulent; after several days it is not unusual to find a gelatinous, ropy exudation which covers the meninges of the brain and cord, especially at the base of the brain. Foster and Gaskell state that the localization of the infection depends upon the stage of the disease—being more pronounced in the vertex in the acute stages, and in the base of the brain in the more chronic cases. As the disease progresses there is a tendency to a tougher, more gelatinous exudation, due to the greater amount of fibrin. On the other hand, the hyperemia becomes less intense in the later stages. In cases lasting from three to four weeks the meninges are edematous and thickened, and there may be bands of organized tissue. The same changes are found in the cord. The brain and cord tissue itself

shows little macroscopical pathology. The tissue is somewhat softer than normal, and there may be small areas of hemorrhage in the brain and cord.

There is practically no involvement of the ventricular system in the early stages of the disease. In patients who die after an attack of several days we find dilatation of the ventricles; this may be marked in the chronic stage. The cranial nerves are usually affected in meningitis, especially the second, fifth, seventh, and eighth—that is the optic, trigeminus, facial, and auditory nerves. The cranial are bathed in the exudate; they are swollen and softened and an intense neuritis may occur.

Eye and Ear.—These organs are frequently involved during the course of meningitis. Councilman, Mallory, and Wright divide the eye lesions into three classes: (1) A neuritis or degeneration of the nerves of the eye due to the involvement of the nerves at the base of the brain; (2) eye lesions due to an extension of the process along the optic nerve; (3) lesions due to neuritis of the fifth nerve and destruction of the gasserian ganglion. The auditory nerve usually shows changes due to the extension of the inflammatory process from the meninges. The labyrinth, cochlea, and the organ of Corti may be involved.

Other Organs.—The involvement of other organs is rare. Meningococcic endocarditis and pneumonia occasionally occur. Kidney and gastro-intestinal involvement are seldom seen. Arthritis, due to meningococcus, is not an uncommon complication of epidemic meningitis.

Microscopical Lesions.—Brain and Cord: Microscopically, the pathologic changes also vary with the stage of the disease. Purulent infiltration in the meninges, with little or no fibrin, is seen in very early cases; the infiltration increases as the disease progresses. A large number of leukocytes of the polymorphonuclear variety are seen. These stain sharply and show an absence of eosinophils. Councilman reports the presence of a leukocyte eight to ten times the size of the normal cell and believes that it is formed from the cells of the connective tissue and lymph spaces. Red blood cells are seldom found. The brain tissue itself shows an infiltration with pus cells which

surround the blood vessels. Further than that, there is seldom any other microscopical finding in the early stages of the disease. Later in the course, changes are found in the ventricles, the surface often being covered with granulations. Little exudation, but a great deal of organized tissue and degenerated leukocytes, are found in chronic cases.

Spinal Fluid.—The amount of fluid is always increased in epidemic cerebrospinal meningitis, unless an obstruction of the subarachnoid space is present. The pressure is constantly increased, ranging between 300 and 700 mm., while Levinson has reported cases in which it was as high as 800 mm. The fluid may be clear early in the course of the disease, but it soon becomes cloudy and remains turbid throughout. On standing, it forms a sediment which changes in character with the development of the disease, becoming more pronounced and thicker as the disorder progresses. As the infection subsides the pellicle becomes less in amount and less firm in consistency. Albumin and globulin are greatly increased in amount—a fact which is demonstrable by the Noguchi, Ross, Jones or Pandy tests. There is a great decrease in the amount of sugar, which, at the height of the disease, may be entirely absent; it returns to normal as the patient improves. Lactic acid and the nitrogen constituents are increased and may be present in large quantities. The colloidal gold reaction does not give a uniformly constant curve and cannot be regarded as an aid in diagnosis. The cells are increased, varying from 50 to many thousand per cubic millimeter of fluid. From 90 to 98 per cent of the cells are of the polymorphonuclear variety. The bacteriological findings are fairly constant. A gram-negative intra- and extracellular diplococcus is found in the direct smear and is also recovered from a culture of the fluid on ascitic dextrose agar.

Symptomatology.—The symptoms of epidemic cerebrospinal meningitis, as in all other forms of meningitis, are due to three factors: (1) To toxins produced by the organism; (2) to increased pressure of the spinal fluid; (3) to the active inflammatory process going on in the meninges and nerve cells. The symptoms are much alike in all varieties of meningitis, whether

due to the meningococcus, the streptococcus, pneumococcus, staphylococcus, or other pus-producing organisms.

Period of Incubation.—The number of cases following direct contact with other cases of meningococcus infection being small, the exact period of incubation of epidemic cerebrospinal meningitis cannot be definitely stated. In few instances in which it was determined, it covered a period of from three to five days. There seems little doubt that the meningococcus may be harbored in the nose and throat for a long time before meningitis develops.

Mode of Onset.—The disease may have a gradual onset, being ushered in with prodromal symptoms such as loss of appetite, malaise, nausea, vomiting, and headache. These prodromal symptoms may last for one to several days before the true nature of the disease is suspected. As a rule, however, the onset is sudden with chill, high fever, vomiting, severe headache, severe pains in back and limbs, and not infrequently convulsions. In early infancy the mode of onset may be quite atypical; all other symptoms except an elevated temperature may be absent.

Temperature, Pulse, and Respiration.—The temperature in most cases of epidemic cerebrospinal meningitis ranges from 101 to 103 F., in others it remains around 105 F. or even higher. There are a few cases in which the temperature remains below 101 F. throughout the course of the disease, and there are rare cases of afebrile epidemic cerebrospinal meningitis. The markedly slow pulse which has so often been described as typical of meningitis and which might be expected from the increased pressure in the cerebrospinal canal, is seldom seen in the epidemic form. As a matter of fact, the pulse is usually not characteristic of the disease. The same is true of the respiration, except in a few cases where it is slow and deep for a brief period, suddenly becoming rapid and shallow, and often changing back and forth many times throughout the course of the disease.

Sensory Disturbances.—Headache, pain in the neck, back, and in the extremities, hyperesthesia, and sensitiveness to light are

common sensory disturbances. While children under two or three years of age cannot of course indicate the presence of headache, their extreme discomfort, restlessness, and moaning lead us to believe that it is present. Older children complain bitterly of pain in the head, which may extend into the back of the neck or beyond to the lower spine. Since pain in the extremities or other parts of the body is seen in all febrile disturbances of childhood, they cannot be regarded as being more characteristic of meningitis than of any other acute febrile disease. Hyperesthesia, when present, is diagnostically important. The slightest pressure upon the legs, arms, or even the trunk is painful and actually distressing to the child. Photophobia may be present in varying degrees.

Motor Disturbances.—Hypertonicity of the muscular system is almost always present in meningitis; in fact it is only in early infancy, or intermittently during the course of meningitis in older children, that this symptom is lacking. This spasticity of the muscular system may be general, so that the legs, arms, and even the feet and hands remain rigidly extended. The abdominal muscles may be taut and, in the absence of abdominal distention or in thin children, the so-called "scaphoid" or boatlike abdomen is seen in a large number of cases. Rigidity and retraction of the neck are present at some time during the course of the disease, with the exception of early infancy, during which time practically all the symptoms may be absent. Opisthotonus, the most extreme degree of rigidity in the neck and back, is seen in the most severe cases; the back being arched so that only the heels and head come in contact with the bed when the patient is placed upon his back.

Convulsions may usher in the disease, then cease only to recur later during the course, or there may be a complete absence of this symptom. Paralysis of any group of muscles may occur, but is usually transient. Paralysis in one extremity may be noted, or there may be a hemiplegia, a paralysis of one side of the face, or a paralysis of the eyelids or the external ocular muscles themselves. Strabismus is a very common symptom, so much so that a child developing this symptom during an

acute febrile disturbance is immediately suspected of having a meningeal involvement. Pupils which are dilated, contracted or unequal, are seen in 90 per cent of children with meningitis at some time during the course of the disease, and are evidence of a motor disturbance within the eye. Tremor may also occur in meningitis.

Mental Disturbances.—Irritability and restlessness, although not diagnostic, are generally more marked in this disease than in the ordinary, febrile disturbances of childhood. Active delirium, up to the point of necessitating restraint, is not infrequently present. Low, muttering, typhoidal delirium or stupor, in which the patient is aroused only by persistent stimuli, is an evidence of extreme toxicity. Insomnia, when present, may be persistent, adding to the patient's distress. Finally complete coma, from which the patient cannot be aroused, may occur and is invariably of bad prognostic significance.

Skin Manifestations.—Cerebrospinal meningitis was formerly also referred to as spotted fever, because of the petechiae or minute hemorrhages under the skin which give it a peculiar spotted appearance. These hemorrhages occur in about 15 to 20 per cent of all the cases, they appear early, within thirty-six hours of the onset, and the diagnosis of meningitis is often suggested by the rash alone. They are particularly prone to occur on flexor surfaces but may be seen anywhere on the trunk, extremities or face. Usually they are very small, varying from the size of a pin-head to three or four times its diameter, although in some cases the hemorrhagic spots may be large in size. They are evidence of blood stream infection with the meningococcus. Herpes has been said to be more common in cerebrospinal meningitis than in some of the other febrile disturbances, and it is frequently seen in various parts of the body, it has, however, no diagnostic significance. A widespread and fleeting erythema occurs now and then, as it does in most acute febrile disorders of childhood.

Gastro-intestinal Disturbances.—Vomiting, due to cerebral irritation, is an outstanding symptom, not only of the epidemic, but of all forms of meningitis. It occurs without any relation

to the feeding; in some cases once or twice daily, in other instances less often. Obstinate constipation may be noted, as well as incontinence of feces, due to the mental condition of the patient.

Bladder Symptoms.—Retention of urine is a symptom that may go unnoticed unless especial care is taken to see that the urine is voided at stated intervals, catheterization being necessary in a certain number of cases. Retention of urine favors cystitis, and it is an open question whether the infection itself adds to the possibility of bladder complications. Incontinence of urine, common to febrile disturbances in children of almost any age, may be expected in the younger patients.

Ocular and Aural Symptoms.—The pupils may be unequal and dilated; this, however, is not a constant sign, as contracted pupils may be found in many cases. Nystagmus, strabismus, ptosis, conjunctivitis, iritis, keratitis, diplopia, or disturbance of vision may be present at some time during the course of the disease. The hearing may be impaired, but this is difficult to determine in young children. Otitis media frequently develops during the acute stage of cerebrospinal meningitis.

Course of the Disease.—As in other diseases in which a specific treatment is administered, the course varies with the promptness and thoroughness with which treatment is instituted. In a typically severe case, the child is seen with a high fever, rigidity of the neck, strabismus, and the other symptoms and physical findings described in this chapter. A lumbar puncture will show a turbid spinal fluid and, without waiting for laboratory confirmation of the bacterial cause, antimeningitic serum is given at once into the spinal canal. Within twenty-four hours the symptoms may be somewhat lessened; in other cases they may not be changed in any way. Usually the temperature shows no inclination to subside at this stage. Within three or four days, following injections of the serum, the temperature becomes lower, the mentality brightens and the physical signs begin to disappear, so that at the end of five or six days—if the treatment is effective—the temperature may be approaching normal and the other symptoms may have entirely disappeared. On the other hand,

a typical case with delayed treatment or without the use of the serum, becomes progressively worse, lasting two or three weeks in the 15 per cent of cases that survive, and finally ending with the pathetic picture of blindness, deafness, hydrocephalus, generalized spasticity, mental deficiency, and even imbecility.

Relapses.—In 1 or 2 per cent of the cases which receive serum, relapses occur. In the untreated cases the percentage of relapses may be as high as 20 per cent.

The infantile type of cerebrospinal meningitis leads to more errors in diagnosis than any other acute disease with which we are familiar, and, unfortunately, it is not a rare condition. In the first year, the only symptom which may be present is an elevated temperature, and it is only on careful physical examination and examination of the spinal fluid, that the diagnosis is made.

The Malignant or Fulminating Form.—This particular variety is characterized by the severity of the symptoms, the tendency to extreme collapse, and the rapid short course. The child may succumb within twenty-four hours, the diagnosis very often not being made unless spinal puncture or autopsy is done. Extensive hemorrhages may take place, not only under the skin but from the mucous membranes as well, in this form.

The Subacute Form.—In the last few years several cases have been admitted into the New York Post-Graduate Hospital, in which the duration of the disease was more than two weeks before admission and the only symptoms were unexplained fever and restlessness. The physical examination revealed nothing characteristic of meningitis and it was only on examination of the spinal fluid that the diagnosis was made. The possibility of meningitis in any child with unexplained fever must be considered.

Physical Signs.—Physical examination of the child may reveal few or no signs at all which would indicate an involvement of the cerebrospinal system. However, in the vast majority of cases, thorough and careful routine examination reveals the diagnosis.

In infancy, a tense, bulging fontanel is almost a constant

finding. When the fontanel is closed, the increased pressure may be demonstrated by a hollow percussion note over the lateral ventricle—this is called the *Maccoven sign* and is of doubtful value. As stated in the discussion on symptomatology, there is a marked hypertonicity of the muscular system in meningitis. This can be demonstrated in various ways: by the stiffness of the neck muscles, by opisthotonos, by Kernig sign, Brudzinski's sign, and the contralateral reflex.

Kernig's sign is present in a large percentage of cases. Kernig noted that a meningitis patient, placed in a sitting position with the thighs at right angles to the body, will invariably flex the legs at the knees. It is usually undesirable to have the patient assume a sitting posture and, for this reason, a modification of Kernig's method is employed. The patient is allowed to lie on his back and an attempt is made to extend the leg at the knee, with the thigh held at right angles to the body. When complete extension cannot be accomplished, it is regarded as a positive Kernig. This sign is not always present, and is especially prone to be absent in infants. In very young infants the *Brudzinski sign* is more likely to be noted. A positive Brudzinski's sign consists of the simultaneous flexion of the thighs and legs on the abdomen when the head is forced forward on the thorax. The *contralateral reflex* may also be observed; that is, when one leg is forcibly flexed, the other may flex also. Brudzinski's reflex is so variable in children that it is not of special significance in this disease.

Deep pressure along the muscles will elicit tenderness, indicating a marked hyperesthesia. The deep reflexes are often increased early in the disease, but they become lost as the condition progresses. However, they may remain normal throughout the entire course of the disease. The cutaneous reflexes are not of any great value.

A tache cérébrale, or urticarial tendency, is due to vasomotor paralysis. Upon scratching the skin a white line at first appears which changes later to a red, raised, urticarial spot. This, however, is more common in tuberculosis meningitis than in the cerebrospinal form of the disease.

Eye Signs.—On examination of the eyegrounds, optic neuritis is not infrequently seen in the chronic basilar cases but is common in the acute stage of the disease. Papillitis, as is seen in intracranial new growths, is very rare. The pupils are often unequal and are apt to vary considerably in size from time to time. Early in the course of the disease they are usually contracted whereas later they may be markedly dilated. Strabismus, nystagmus, and ptosis are not uncommon. Ulceration of the cornea is unusual and indicates involvement of the fifth nerve.

Ears.—Redness of the drums is not infrequent and in a large percentage of the cases signs of acute purulent otitis media are seen.

Paralysis.—As stated under symptomatology paralysis of any group of muscles, may occur but this is usually transient. Paralysis is especially prone to occur in the face or eye muscles.

Cutaneous Signs.—The hemorrhagic eruption of cerebrospinal meningitis varies according to the nature of the epidemic and the severity of the infection. It may be present in only a small percentage of cases in one epidemic and extremely common in another. When it does occur it is a valuable aid in diagnosis. The erythematous and herpetic eruptions which may occur are not characteristic of the disease.

Blood.—In all cases there is a leukocytosis. This is of the polynuclear type and ranges from 15,000 to 50,000 per cubic millimeter. Blood culture reveals the presence of the meningococcus in 30 to 85 per cent of the cases.

Urine.—As in any other acute infectious disease the urine may show a trace of albumin and a few casts. In few cases blood is present.

Temperature, pulse, and respiration are not of any especial diagnostic value.

Diagnosis.—The symptoms and physical signs of meningitis—in all its forms—are not constant; many of the symptoms may not be present through the entire course, and one symptom may be prominent one day and utterly lacking the next; while this is true in any disease, it would seem as though the variations are greater in meningitis than in other diseases.

The diagnosis rests especially upon the sudden severe onset, in which headache, vomiting, convulsions, restlessness, stiffness, and pain in the neck are prominent features. All of these symptoms are indications of an involvement in the meninges, either directly or reflexly, by the action of toxins produced during an acute disease.

The diseases which may simulate meningitis during infancy and early childhood, and from which it must be differentiated, are numerous. One must always be on guard, as many diseases are ushered in with symptoms pointing to the cerebrospinal system. Systemic diseases such as pneumonia, typhoid, the exanthemata, and gastro-intestinal conditions, in which there is no true inflammation of the meninges, may nevertheless show well-marked meningeal symptoms. These may be present at the onset of the disease or may develop during its course. In suspicious cases it is advisable to do a lumbar puncture. This procedure, when properly performed, is not a harmful one, and may be the only method by which a true diagnosis can be made.

Cerebrospinal meningitis must also be differentiated from other diseases which involve the meninges—such as tuberculous meningitis, septic meningitis, poliomyelitis, and epidemic encephalitis. In these conditions the clinical picture closely resembles that of cerebrospinal meningitis. It is possible in most instances to differentiate these disorders only by a careful, thorough examination of the spinal fluid. The accompanying chart will serve to indicate the distinguishing features of the fluid in these various diseases.

The final diagnosis, after all, depends upon the lumbar puncture except in the most typical cases, and even here a meningism may stimulate a meningitis so accurately that only by means of an examination of the spinal fluid will it be possible to differentiate the two conditions. For example, the symptoms and physical signs of meningitis may appear during the course of pneumonia, but only with the aid of a lumbar puncture will one be able to reveal the presence or absence of increased cells and organisms in the spinal fluid.

	Organism.	Color.	Amount.	Pressure.	Sediment.	Globulin.	Cells	Sugar.	Lactic acid
Meningism.	None.	Clear.	Increased.	Increased.	None.	Normal.	Normal or slightly increased.	Normal.	Normal.
Epidemic encephalitis.	Minute filtrable virus described by some authors.	Clear.	10-30	Increased.	None.	Increased.	10 to 20 small mononuclears.	Normal.	Normal.
Anterior poliomyelitis.	Micrococcus described by some authors.	Clear.	Increased.	Increased.	None.	Increased.	10 to 100; polymorphonuclears very early; mononuclears after second day.	Normal or slightly increased.	Normal
Tuberculous meningitis.	Tubercle bacilli.	Clear or slightly opalescent.	Increased.	Increased.	Fine pellicle.	Increased.	30 to 400.	Decreased.	Increased.
Meningococcus meningitis.	Meningococcus.	Turbid.	Increased.	Markedly increased.	Thick, varying with stage of disease.	Increased.	50 to 80,000; 95 per cent polynuclears, endothelial cells present.	Decreased or absent.	Increased.
Pneumococcus meningitis.	Pneumococcus.	Turbid.	Increased.	Increased.	Present.	Increased.	50 to 56,000; 98 per cent polynuclears.	Decreased or absent.	Increased.
Streptococcus meningitis.	Streptococcus.	Turbid.	Increased.	Increased.	Present.	Increased.	50 to 50,000; 98 per cent polynuclears.	Decreased or absent.	Increased.
Influenza meningitis.	Influenza bacillus.	Turbid.	Increased.	Increased.	Present.	Increased.	50 to 50,000; 98 per cent polynuclears; 50 per cent lymphocytes.	Decreased or absent.	Increased.

Complications and Sequelae.—*Complications.*—The most common complications occurring in meningitis are otitis media, bed sores, severe herpes, conjunctivitis, keratitis, and hydrocephalus. Hydrocephalus is invariably due to a blockage of the cerebrospinal fluid of adhesions. Other complications, such as the following, may occur, arthritis, nephritis, pleurisy, pericarditis, endocarditis, peritonitis, parotitis, enteritis, pyelitis, cystitis, phlebitis, optic neuritis, urticaria, erythema, epididymitis, pemphigus, subcutaneous abscesses, ankylosis, embolism, strabismus, and nystagmus.

Sequelae.—According to statistics drawn from many authorities, 18 per cent of all cases of meningitis develop sequelae. Of these, about 42.6 per cent result in deafness.

Next in order of frequency is paralysis, seen in 18 per cent of the cases. This may be of various kinds—namely, facial paralysis, monoplegia, diplegia, hemiplegia, paraplegia, or strabismus.

Mental disturbances (usually a deficiency) occur in 13.1 per cent; defects of vision in 11.5 per cent; speech defects in only 3.3 per cent; hydrocephalus in 1 or 2 per cent of the cases.

Prognosis.—Until the introduction of the antimeningococcus serum, the prognosis of this disease was usually bad; the mortality varying in different epidemics from 50 to 100 per cent, the average being 70 per cent. Permanent sequelae were observed in more than 70 per cent of the cases which recovered. Since the introduction of serum therapy the mortality has been greatly reduced. Flexner reported a mortality of 30 per cent in a series of 4300 cases treated with serum. The mortality reduction has been especially observed during epidemics of meningitis.

The prognosis depends upon the following factors: the severity of the disease, the age of the patient, the stage of the disease at which the treatment is instituted, and the potency of the serum employed.

Recently, in New York Post-Graduate Hospital, this last factor was clearly shown to be a most important influence in the prognosis. Until a potent serum was found the mortality was 100 per cent in a group of 13 cases treated. Upon obtaining and using a potent serum, it was reduced to 12 per cent in a

series of 40 cases occurring in the same epidemic. It therefore follows that when the strain of meningococcus in question is resistant to the serum which is being used, one should not conclude that it is resistant to all serum treatment. In the event that no improvement is noted after several injections of serum, another serum should be substituted. This applies not only to cases occurring in epidemics, but also to sporadic cases. It is an undisputed fact that the earlier the treatment is begun, the better the prognosis and the fewer the sequelae.

On the whole, the mortality has been found to be much higher in infants than in older children.

Neal, in a series of 500 cases, reports the following list of complications and sequelae:

Respiratory:

Pneumonia	19
Pleurisy	1
Influenza	4

Urinary:

Cystitis	2
Arthritis	13
Secondary Infection of the Meninges	7
Meningeal Hemorrhages	5
Brain Abscess	2

Paralysis:

Hemiplegia	6
Facial	6
Speech	3
Not Classified	7
Headaches	3
Mental Deficiency	1
Delirium during Convalescence	2
Forgetfulness during Convalescence	1
Hydrocephalus	9

Eye Conditions:

Ptoxis	4
Strabismus	30
Blindness	3
Conjunctivitis	5
Iridochoroiditis	12
Exophthalmos	1

Ear Conditions:

Deafness	29
Otitis Media	4

Treatment.—*Prophylaxis.*—The method of transextension of the disease is not known and therefore preventive treatment is almost impossible. It is desirable to observe individual precautions in the management of the disease, but seldom does a case of meningitis develop in the same ward where there are other meningitis patients.

General Treatment.—As with other diseases, the patient should be kept in a large well-ventilated room. If there is any evidence of photophobia the room should be darkened. The diet should consist first of liquids; later, as improvement is noted, a soft diet should be given, if necessary gavage feeding should be used. General care in the form of alcohol sponge baths, mouth toilet, and colonic irrigations should be given as indicated. Sedatives such as bromides and codeine are to be administered if the patient is extremely restless. In short, the general treatment of epidemic cerebrospinal meningitis should be symptomatic. Cardiac stimulation may become necessary, and if so, digitalis and caffeine sodium benzoate, adrenalin chloride, or camphor in oil should be employed. Strychnine is contraindicated.

Meningitis is a serious illness by reason of the vital nature of the structures involved and the irregularity of the course of the disease. The important factors in the treatment and mortality of the disease are the severity of the infection, the age and resistance of the patient, the stage at which treatment is begun, the potency of the serum, and the method of treatment. It is a well-known fact that the earlier serum treatment is started, the better is the prognosis.

Specific Treatment.—In every suspicious or doubtful case of meningitis, a lumbar puncture should be done immediately and serum should be given if the fluid withdrawn is cloudy. During an epidemic, serum should be administered in every early case in which there is a strong suspicion of the disease, even if the fluid is clear. The amount of spinal fluid allowed to run out should depend entirely upon the degree of pressure manifested. It is a good rule to allow the fluid to drain until the pressure is reduced to normal. The pressure may be estimated as approximately normal when the rate of flow is from 10 to 15 drops per minute.

The amount of serum to be given should be 4 to 5 cc. less than the amount of spinal fluid withdrawn.

In the early days of serum therapy of meningitis, the serum was given intraspinally at intervals of twenty-four hours and usually in doses of 20 cc. except in severe cases when it was given about every twelve hours. This method of treatment as originally outlined by Flexner was followed until about 1918 when a movement toward a more "intensive" plan of treatment developed. Some authorities about that time advocated intraspinal injections of serum every eight to ten hours combined with intravenous and intramuscular injections of serum. Our experience has been that the conservative of serum gives better results than the intensive treatment. The more conservative program is to administer the serum intraspinously not more often than once daily. The serum should be used intravenously or intramuscularly only in selected cases, cases which show a persistent meningococcemia, and in cases of meningococcic septicemia without meningitis. The intravenous administration of serum is not without danger as a severe or even fatal reaction may possibly occur.

The potency of the serum is a most important consideration. Serum may be used with good results in certain cases and prove ineffectual in others. When no results are obtained, it is logical to suspect that the particular strain of the organism causing the infection is resistant to the serum employed; in this event, another should be used.

In the event of block, the serum must be given intraventricularly or in the cisterna magna. It may be administered to infants intraventricularly; however, if the fontanel is closed the serum may then best be given into the cisterna magna. This latter measure has ceased to be regarded as especially dangerous and should be resorted to whenever there is evidence of block and the fontanel is closed.

Quantity and dose of serum to be employed: It is safe to say that one should never give less than four or five intraspinous injections. The dose of serum is usually 20 cc. if as much or more spinal fluid has been withdrawn. Daily consecutive doses

should be given until there is a clinical improvement as manifested by a drop in temperature and improvement in the general condition. With improvement, the spinal fluid will show a decrease in cell count, an increase in spinal fluid sugar, a decrease in lactic acid, and a disappearance of the organism from the spinal fluid. It is absolutely necessary that serum be given daily intraspinaly until two successive specimens of spinal fluid show no organisms by smear or culture. After improvement has been noted, serum should be given every other day until there is a disappearance of practically all symptoms. It is often necessary to do several lumbar punctures during convalescence for the relief of pressure, and these fluids should be carefully examined as the return of organisms would indicate additional serum treatment. It is impossible to state the exact quantity of serum which should be given. Cases requiring as little as 90 cc. and as much as 1300 cc. have been reported. The average amount used in our series of cases in 1928 was 245 cc. The serum should be slightly warmed, and should always be given by the gravity method, allowing it to flow very slowly.

The results are often immediate and surprising. In many cases there is a marked clinical improvement with a drop in temperature, and the patient becomes much more comfortable. Sometimes a mild or severe reaction follows the administration of serum. This is seldom encountered, however, and is usually temporary. As with other horse sera, urticaria or other anaphylactic phenomena may develop after several days. Very little improvement with serum therapy is to be expected after the acute stage has passed, as the symptoms are then due chiefly to the effects of distention of the ventricles caused by a chronic basilar lesion. However, except in the extremely chronic cases, serum therapy should be tried.

Relapses may occur, as indicated by a rise in temperature, an increase in the cell count, reappearance of organisms in the fluid, and an aggravation of the symptoms. A recurrence is evidence that the meningococci are still present and active; therefore, serum treatment should be instituted again. It is essential that a relapse be differentiated from the development

of an acute complication or the condition which may occur as the result of too prolonged treatment. In these instances, although the temperature remains high and the cell count may be increased, no organism is found and the spinal fluid sugar and lactic acid are quite normal in quantity.

There are great variations in the therapeutic value of different sera. Unfortunately we have no laboratory test that measures the difference and as a result a great deal of serum has been used that although it passed accepted standards was absolutely ineffective clinically. The curative action of the serum is not due to a general protein reaction but lies in increasing the phagocytic power of the cells or in so affecting the organisms that they may be more easily ingested by the cells. Serum injected intraspinally remains in the subarachnoid space for about twenty-four hours and it is probably that in doing a spinal tap oftener than once in twenty-four hours we may remove cells that had been stimulated to a high degree of phagocytic power.

Formerly the agglutination test has been accepted as an index to the curative value of a special serum against a specific strain of meningococcus. In a series of 44 cases observed at the Post-Graduate Hospital, we have found it entirely inadequate. This observation is not surprising, inasmuch as other methods—such as the opsonic index and the complement-fixation test—have likewise proved to be of no value in this connection. The therapeutic test appears to us to be the only reliable method of determining the curative value of a serum.

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SKIN TUMORS: WITH SPECIAL REFERENCE TO PRE-CANCEROUS DERMATOSES AND THE GROUP OF MYCOSIS AND RELATED CONDITIONS

FOR practical purposes, in considering both their nature and management, skin tumors may be classed as identical with skin neoplasms. Usage has dulled the sharp etymological distinction between the two words, the term of greater content having absorbed the other. It is far easier to define a tumor than a neoplasm. It is easier to be sure that tissue is abnormal than to be sure that it is new. Roughly, any skin abnormality made up of massed cells, however small the lesion may be, is histologically a tumor if the cells are not inflammatory. Usage, again, has favored the belief that noninflammatory tissue is neoplastic. As a matter of fact, it may be archeoplastic, to coin a word, a cellular echo such as may explain many nevi. Or it may be heterochthamous, misplaced tissue. More than this, a tumor may stimulate about itself an inflammatory reaction often making it difficult to find the tumor elements in the midst of the inflammatory ones. So I prefer the word tumor in the title of this brief article, because in spite of its limitations, it embraces growths of all origin except inflammatory.

This outline is not going to be dermatological in spirit. In scores of volumes and thousands of shorter articles the descriptive aspects of skin tumors are discussed. So there would be little excuse for adding to the plethora. The important point to emphasize is malignancy in skin tumors. Since this cannot be done without reference to so-called "benign tumors," the scope of the present essay must be increased to include these. More-

over, the subject is skin tumors, wherefor tumors of the visible mucous membrane and mucocutaneous borders are excluded. The reason for this is because these two groups may owe their existence to excitation different from that conditioning the purely cutaneous ones. The interesting metaphysical question of the ultimate cause of tumors is not within the purview of this paper. Nevertheless, one phase of etiology will be considered, namely, whatever is embraced in the term "precancerous." This term has insinuated itself into the vocabulary as a clinical designation, an intellectual disadvantage even though it stated a fact. That it states a fact seems questionable to me.

Skin tumors are benign or malignant and in both groups there are growths arising from connective tissue, epithelial tissue or from tissue not easily identified, which may be archaic, or may reflect embryonal rests or misplacements. Certain tumors may have their ancestral roots in the reticulated endothelial system. Very few cutaneous tumors are malignant in the manner of visceral, mammary, labial or lingual cancer. On the other hand, melanomata and some sarcomata of the skin are highly malignant. This question will be dealt with in its proper context, for malignancy is a practical matter as well as a matter of definition.

Before proceeding with the more important questions already alluded to, it would be well for the reader to glance at the subjoined table (Table 1) in order to realize the number and variety of skin tumors, and to get a rough conception of their divergencies and tangencies. To facilitate this the following thumb nail sketch is interpolated. Benign epithelial growths (A. I., 1-7) include, in numerical order, the common wart, the multiple flat juvenile wart, the plantar wart, the senile or seborrheal wart, and the senile keratoma. All arise from activity in the rete pegs, with or without scaling, but in any case with marked hyperplasia of the corneous layer. The last two will be more fully discussed in connection with epithelioma. Benign connective tissue growths (A. II., 1-6) arise, following the order of the table, from fibrous connective tissue, smooth muscle (the arrector pilaris fibers), the subcutaneous fat, fatty change in the connective tissue fibers and fatty change in the fibers of the

TABLE 1
SKIN TUMORS

(A) Benign.	I. Epithelial.	<ol style="list-style-type: none"> 1. Verruca vulgaris. 2. Verruca plana juvenilis. 3. Verruca plantaris. 4. Molluscum contagiosum. 5. Condyloma accuminatum. 6. Verruca senilis } Also (B. 7. Keratoma senile } I., 5.)
	II. Connective tissue.	<ol style="list-style-type: none"> 1. Fibroma—simple, Recklinghausen. 2. Myoma. 3. Lipoma. 4. Xanthoma tuberosum. 5. Xanthoma planum.
(B) Malignant.	I. Epithelial.	<ol style="list-style-type: none"> 1. Epithelioma basocellulare. 2. Epithelioma spinocellulare. 3. Epithelioma intra-epidermoid. 4. Metastatic. (Also group B. IV.) 5. Precancerous dermatoses. 6. Paget's disease of the nipple. 7. Paget's disease, extra-mammary. 8. Cancer en cuirasse. 9. Xeroderma pigmentosum. 10. Roentgen-ray cancer.
	II. Connective tissue.	<ol style="list-style-type: none"> 1. Round-cell sarcoma. 2. Spindle-cell sarcoma. 3. Angiosarcoma. 4. Kaposi's sarcoma. 5. Lymphosarcoma. 6. Mycosis and kindred conditions (B. III.).
	III. Reticular endothelial.	<ol style="list-style-type: none"> 1. Mycosis fungoides. 2. Leucemia cutis. 3. Hodgkin's disease. 4. (Lymphosarcoma.)
	IV. Metastatic tumors of noncutaneous or cutaneous origin.	<ol style="list-style-type: none"> 1. Visceral carcinoma. (Also group B. I., 4.) 2. Sarcoma, including hypernephroma and chloroma. 3. Melanoma arising in the skin or elsewhere. 4. (Group B. III., 1-3.)

orbicularis palpebrarum. I am purposely omitting colloid milia and some other rare conditions, in order to gain space for matter of more importance from the standpoint of this paper. Flat juvenile warts are probably parasitic in origin; xanthoma and xanthelasma are in some way related to disturbed lipid metabolism. Each of the five connective tissue tumors has a characteristic histologic appearance which is of diagnostic significance in lesions which are clinically not easily classified.*

Malignant epithelial tumors (B. I., 1-11) fall into two main types (B. I., 1, 2) the basal cell and prickle-cell epithelioma. The first of these is the bridge between benign and malignant tumors, and it would be difficult to disagree with either preference. Convention, however, regards them rather as malignant. There is a distinct relationship, in the minds of many writers, between epitheliomata of this description and senile warts and keratomata (A. I., 4, 5). The intra-epidermoid lesion seems to me to be a variant of the basal cell type. Precancerous dermatoses will be emphasized below. Paget's disease of the nipple is really, as Fraser has recently redemonstrated, a manifestation of mammary carcinoma arising in the lacteal ducts. Extra-mammary Paget's disease, if there be such a thing, apparently arises from the sweat ducts. Cancer en cuirasse is indeed cancer. Xeroderma and roentgen-ray cancer will be fully dealt with below.

Sarcomata of the skin are like sarcomata anywhere else. But one type, the multiple benign hemorrhagic sarcoma of Kaposi, is peculiar. Its name describes it. It is more frequently found in the Hebrew than in other races and the adjective "benign" is inapplicable save in a relative sense. As Gilchrist and Ketron showed it may terminate as true sarcomatosis. Moreover, whether the patient sustains the disease only five or ten years, or as much as twenty, the fatal issue is due to metastasis, however deliberate the course. Lymphosarcoma is the connecting link between mycosis, leucemia, and Hodgkin's disease of the skin (B. III., 1-3) and sarcomata, in

* For the description features of these lesions, as well as the malignant ones, any good text-book on Dermatology may be consulted.

the minds of those who regard the last three as sarcomata. These conditions certainly form tumors, and will receive especial consideration below.

It is apparent that skin tumors arise in many ways; from infection (warts, molluscum contagiosum, condyloma accuminatum); from irritation (plantar warts); from tissue alterations probably reflecting metabolic disturbances (A. II., 1-5); from local tissue disturbances, embryonal rests, nevi, sustained irritation (B. I., 1-10, and B. II., 1-5); from reticular endothelial disturbances (B. III., 1-3) and from growths elsewhere in the body (B. IV., 1-3). A discussion of the evidence for the beliefs set forth in the foregoing would form, alone, a longer essay than this may be. Thus from a wealth of interesting material the following questions will be selected for elaboration: malignancy, precancerousness, including the relationship of nevi to tumors, and the nature of reticular endothelial growths. Finally, a short passage on the principles of diagnosis and treatment of skin tumors will be added.

A growth is malignant that tends to recur after removal or destruction, that metastasizes and kills. This, briefly, is the conventional definition. In the main it is generally apropos, except as to the skin. Examining each element in the definition, so far as cutaneous tumors are concerned, it is found to have general significance only in selected types. Basal cell epithelioma (malignant) rarely recurs; simple and plantar warts (benign) often do. Perhaps this obstinacy is in part due to incomplete removal or destruction, perhaps to sustained irritation. Benign connective tissue growths are hard to get rid of at all, and in xanthoma tuberosum (if these be strictly tumors) and Recklinghausen's disease, the effort is fruitless. Prickle-cell epithelioma tends to recur, but does not often metastasize, whereas the xanthoma and Recklinghausen's disease present numerous lesions. On the other hand, Paget's disease of the nipple, cancer en cuirasse, xeroderma pigmentosum, roentgen cancer, and many of the sarcomata (B. II., 1-5) metastasize and are fatal. The same is true of the endothelial growths (B. III., 1-4) and the melanoma. Obviously skin metastases from remote growths are fatal in the

measure the stem growth is and have no bearing on this discussion. Of all malignant growths of the skin only two are common, the epitheliomata, and these are not directly malignant in the defined sense of the word. But the prickle cell growth, so far as the patient is concerned, is malignant, since, if incurable, it relentlessly progresses and may destroy the eye, lips or nose, death resulting from incidental disturbances. Thus of twenty-one kinds of malignant growths of the skin, seventeen are malignant in the precise sense but these seventeen scarcely include one tenth of all cases of malignant skin tumors seen by physicians. At one end of the scale is the basal celled growth which is never fatal, at the other the melanoma which always is. In between are all the other conditions enumerated, which, though fatal, run long courses and present nuances of malignancy, if such a phrase is permissible, that divest malignancy in skin tumors of a great deal of the horror inherent in growths in other terrains. It is clear that malignancy is biologically a definite concept but in practice a malignant growth may be essentially benign, as the basal cell epithelioma, or a benign or only slightly malignant tumor may incidentally be serious if it invades important structures, such as the eye. From the human standpoint such a lesion would be malignant.

Precancerous skin lesions, whatever their composition, are nonmalignant forerunners of malignant ones. The concept means just this or it means nothing. The term was introduced by Dubreuilh nearly forty years ago and was quickly acclaimed. In the course of time about twenty conditions were reported, the lesions of which more or less frequently resulted in epithelioma. Twenty years ago Bowen described what he called the precancerous dermatosis. It followed a consistent slow course, many of the numerous lesions in his case becoming epitheliomata. Similar cases were reported by Darier in France and by me in New York, with further additions by Bowen himself, and other American authors whose studies were mainly of cases they thought were like Bowen's but which did not rigorously conform to his original description and which were probably senile warts or senile keratomas. The concept grew so extensive as to cease

to have what little meaning it first had. Finally the term acquired the jingle significance conferred on so many medical designations and was used *faute de mieux*. Eller revived the almost pulseless issue involved by rewriting the old story under the title of cancer supervention in skin diseases. This led me to examine the data with more care than I ever had before. I read a report on my results in May, 1932, before the American Dermatological Association, which Dr. Pusey found he could not publish in the Archives of Dermatology because of lack of space and because he considered the question dialectic. What is dialectic and what is not may be a matter of opinion but it seems to me that argument supported by demonstrated fact, as will be shown below, scarcely can be so characterized.

As stated at the beginning of the preceding paragraph, precancerous skin lesions can only mean nonmalignant forerunners of malignant ones. What can "cancer supervention in skin diseases" mean? It can only mean the supervention of cancer in previously nonmalignant lesions. In short the newer phrase simply inverts the terms of the older one. It is not intended to devote this essay to questions of verbiage save to state that a designation of the sort being considered, implying as it does a declaration of belief as to etiology, must have more than assumptive value for its justification. To have merit a belief must be supported by fact. What is the fact?

The table about to be set forth is transcribed from my paper on the present theme published in the Journal of Cancer Research (I., 3, July, 1916).

Table 2 attempts to classify the alleged provocatives. Table 3 does not. Were I to construct a table today, assuming the idea of precancerousness appealed to me, it would resemble neither of these. I should throw out mucous membrane lesions for separate consideration. Bowen's disease, Paget's disease of the nipple, xeroderma pigmentosum, are frankly cancer and hence obviously not precancerous. I should retain for consideration moles, keratoma senile, lupus scars, skin horns, and sebaceous cysts. All the rest I should exclude either because of rarity (kraurosis vulvae, arsenical keratosis) or because the lesions are

TABLE 2

(A) Congenital.	I. Malformations—Nevi.
	II. Dystrophies—Xeroderma pigmentosum.
(B) Acquired.	I. Inflammations.
	1. Hyperkeratoses.
	(a) Seborrhoeal keratoma.
	(b) Inveterate psoriasis.
	(c) Leukoplakia.
	(d) Horns.
	2. Specific inflammations.
	(a) Lupus vulgaris.
	(b) Lupus erythematosus.
	Ulcers and fistulae.
	3. General inflammations.
	II. Physical agents.
	1. Exposure—Sailor's skin.
	2. Actinic rays—Roentgen carcinoma.
	III. Chemical agents—Arsenic, paraffin, soot.
	IV. Regressive changes—Senile keratoma.
	V. Malformations—Dermoid cysts.
	VI. Scars from any cause, notably syphilis, lupus and burns.
	VII. Unclassified—Paget's disease.

TABLE 3

Transcribed from Eller's article (British Journal of Dermatology, Vol. XVII, June, 1930, pp. 263-289)

Syphilis.....	Lupus erythematosus.
Radiodermatitis.....	Chronic ulcers.
Leukoplakia.....	Paget's disease of the nipple.
Moles.....	Cicatrices (also burns).
Senile and seborrhoic keratoses.....	Cutaneous horns.
Kraurosis vulvae.....	Bowen's disease.
Occupational keratoma.....	Extramammary Paget's disease.
Lupus vulgaris and tuberculosis cutis...	Papilloma of tongue.
Arsenical keratoses.....	Xeroderma pigmentosum.
Sebaceous cyst.....	Elastomycosis.
	Inflammatory dermatoses (psoriasis, lichen planus, eczema).
	Keratosis follicularis.

so common (lupus, burns, psoriasis, lichen planus, eczema) that an occasional cancer arising in one of them could obviously have no general significance. One state, radiodermatitis, I should reserve for special consideration. Without constructing such a scheme I shall adhere to its spirit in the immediate analysis.

Undoubtedly some moles, notably among the pigmented variety, result in melanoma. This is highly malignant and almost invariably fatal, irrespective of treatment. Considering the millions of pigmented moles the billion or more adults populating the world have, to say nothing of the other billion who are children and adolescents, the incidence of melanoma is indeed trifling. Keratoma senile at times is the forerunner of epithelioma. A rich literature deals with the subject in relation to the senile keratoma, compared with or contrasted to the seborrheal wart and the relationship of these to malignancy. Certainly these lesions occur at the cancer age. Equally certainly it is rare for one of them to become malignant. Hazen says 5 per cent do; other authors give slightly greater or smaller figures. Lupus vulgaris scars, according to Eller's summary, lead to malignancy in 1.5 to 4 per cent of instances; sebaceous cysts in a trifle under 5 per cent and about 12 per cent is the figure for cutaneous horns. Excepting the last two, it seems to me as likely that early epithelioma mimics these conditions as that these conditions are forerunners of epithelioma. In any event, the figures are trifling. Since injuries and sustained irritation have something to do with the causation of epithelioma, it is not astonishing that lupus scars should be among them. As to sebaceous cysts, I doubt the figures but have not yet studied them exhaustively. The belief in connection with cutaneous horns is ludicrous. I have never seen a cutaneous horn unrelated to malignancy and I am sure that the horn develops on the epithelioma as an expression of exaggerated keratinization. In short, it is the epithelioma which is precornuous. This term will undoubtedly delight the cult who worship the prefix "pre."

The changes wrought in the skin by overexposure to the roentgen ray certainly often lead to epithelioma. These changes are similar to those produced by exposure to the sun and weather in sailors and farmers, resulting in the familiar sailor's skin. In xeroderma pigmentosum a similar state is inborn. Thus the last may be regarded as the precocious form, sailor's skin as the naturally produced form and x-ray skin as the artificially produced form, of the same thing. This is the one and only group

at once presenting a persistent relationship to epithelioma and supplying a clue to the etiology thereof. In a word, in these three allied conditions may be discerned an integument predestined to malignancy. If it must be, such a skin may be called precancerous, though what is thereby gained I cannot perceive, or, when epithelioma appears in such a skin, the growth may be called supervensive, which is another way of stating that the growth happened.

It is known that the skin of individuals from approximately forty years old up oftener develops cancer than in earlier life. It is also known that in xeroderma the skin is prematurely senile. It is likewise known that overdosage with the roentgen ray accelerates the aging of the skin. From its very name, keratoma senile, we know that this condition is a phenomenon of age. Before forty, except as to xeroderma and roentgen skin, epithelioma is unusual; before thirty it is rare and before twenty almost unheard of. Thus we may fairly assert that the skin from the prime of life on is liable to epithelioma. The only justification for the term "precancerous" would be its employment in this sense and as to the state of the skin itself, but not as to individual lesions that did not resemble cancer grossly at the start, but were found to be cancer nevertheless. To add that a cancer, under such criteria, were supervensive would be to utter a platitude, for of course it supervened or it would not exist. A little knowledge of biology and a little feeling for the meaning of words on the part both of writers and readers would go far to unburden medical thought and speech of encumbrances.

Without any stereotyped or artificial classification of alleged forerunners, an epithelioma is recognized by its behavior and gross and microscopical appearance. It starts as a small scaling, pink, yellow or brown lesion. As a rule it grows slowly, requiring years to attain appreciable enlargement. The scale generally adheres and, when forcibly removed, leaves a bleeding surface. The margin tends to be elevated, but is not always so. Some lesions ulcerate centrally, others atrophy and both kinds scar. The picture is one of a growing papule resembling at times the senile wart, the seborrheic wart, annular lichen planus, a gran-

uloma or what not. Those who do not believe these are cancer from the outset call the lesions precancerous. Microscopically an epithelioma looks like an epithelioma. In doubtful cases only this last criterion has value. Thus a chronic, growing lesion, prevailingly found on the face, more often found singly than in numbers (excepting Bowen's disease, senile keratoma and the group discussed in the paragraph before last) is epithelioma, subject to microscopical corroboration. This conception requires no pedantry, remote hypotheses, exotic verbiage nor anything but objective recognition by the unaided and aided eye. Regional adenopathy and metastases are rare in cutaneous epithelioma. Cutaneous epithelioma is rarely malignant in the sense that cancer in other tissues is. The exceptions are found mainly in xeroderma pigmentosum and roentgen skin.

Undoubtedly the slow growth of epithelioma, the clinical similarity of its early stages to lesions of other skin disturbances, gave the first impetus to the concept of precancerousness. I believe Bloodgood asserted that in just short of 1000 cases of epithelioma of the skin and visible mucosae he could find none without the history of a preexisting lesion. After all, such a belief must be based on the patient's statement in a large measure, and it is questionable if the patient's clinical acumen would be a guarantee that the alleged precursor was not already an epithelioma. Moreover, in general, the patient's story of such a lesion is one of "a pimple, with a little piece of skin on it, that bleeds when you take it off, or shave it, or rub it." If this is valid evidence of a precancerous lesion, my contention falls. With this idea in mind, I investigated the matter for myself, with perhaps far too limited material, that in Table 4, from the New York University Clinic, having been given me through the kindness of Dr. Howard Fox; that in Table 5 being derived from carefully observed cases of my own.

In other words these tables indicate that three quarters of the patients gave no history or objective evidence of preexisting lesions, while a tenth more gave no objective evidence of such lesions, the anamnestic factor remaining in doubt. Only one seventh of the patients gave objective evidence of, or alleged

forerunners of their epitheliomata. Without overemphasizing irrelevant details, forty of the lesions in the clinic group were basal cell, the remainder prickle cell growths and just under 60 per cent of the patients were men.

TABLE 4
ANALYSIS OF CLINIC CASES

	Preexisting conditions.	Spontaneous origin.	Doubtful.
	Sebaceous cyst 1, "mole" 2, senile keratosis 6, seborrheal keratosis 1.	60	1
Totals.	10	60	1
Percentage. Eliminating nevi.	15% 12%	85% 88%	

The only deduction that suggests itself to me from these findings is that the skin itself is "precancerous" or that epithelioma "supervenes" in the skin. If an epithelioma develops, of course it is due to predisposition, but what the nature of this

TABLE 5
ANALYSIS OF PRIVATE CASES

	Preexisting conditions.	Spontaneous origin.	Doubtful.
	Sebaceous cyst 2, mole 1, melanoptic mole 1, senile keratosis 1, seborrheal keratosis 1, comedones 1, wart 1.	20	10
Total.	8	20	10
Percentage. Eliminating moles.	21% 28%	53% 55%	26% 27%
Combined totals. Both tables eliminating nevi.	14 or 13½%	80 or 76½%	11 or 10½%

predisposition may be is not illuminated by words like the two in quotation marks in the previous sentence but rather by phenomena consistently present in xeroderma, roentgen skin, sailors' skin and senile keratoma, namely alterations in the collagen and elastic tissue and referable to aging, whether in

the natural course of events or artificially induced. If such changes occur in an individual who also has psoriasis, lichen planus, lupus erythematosus, a sebaceous cyst or scars, what is surprising in the epithelioma's developing occasionally in one of the lesions of the unrelated disease? The coincidence is so rare, considering the commonness of these diseases, that it can be only fortuitous.

Charles Singer, in *A Short History of Medicine* (Oxford University Press, Amer. Br., p. 360, 1928), says: "If from facts no laws emerge, the facts themselves become an obstacle, not an aid, to scientific advance." I see no reason to regard the concept of "precancerousness" or kindred concepts as even approximating facts, but if they are, what "laws emerge" from them? None at all. Without giving the observations any names, a clinician knows from experience when to suspect the presence of an epithelioma, whether it arises in previously normal or abnormal skin; and this is all he needs to know. But he cannot be sure of himself without microscopical verification. These two sentences tell the whole story of the diagnosis of epithelioma. To say more than this is what Hamlet called "words, words, words." Then what possible sense can there be in the terms "precancerous lesions" and "cancer supervention"? I cannot supply the answer. They throw no light on the fact of whether a cancer is present or not; on its origin, its nature, its degree of malignancy, nor on any other facet of the question which alone justifies the adoption of new members in the, shall I say scientific, vocabulary. Far be it from me to suggest that dragging a red herring across the trail subserves purposes of materialism. I should be loath to believe any physician so disingenuous.

Another short paragraph, and we will pass to the next phase of this essay. Pigmented moles may be the origin of a highly malignant type of growth—the melanoma, which resists treatment, metastasizes, and is fatal. The numerous biological problems involved, the nature of the type of mole, the kind of pigment in it, the relation of the pigment to the Dopa reaction and kindred questions, in themselves would prolong the discussion beyond reasonable proportions. Such a mole is literally

precancerous in the sense that it is far likelier to produce a melanoma than unpigmented skin would be. Any sort of trauma to such a lesion is potentially dangerous. Without blatant optimism, however, let it be pointed out that there must be over a quarter of a billion pigmented moles in the United States, and that nevertheless melanoma is happily rare. If one tenth of them became malignant, melanoma would be as common as psoriasis. Somewhere between utter indifference to preventive medicine and hysterical emphasis on the consequences of ignoring a freckle, is the happy medium. Americans might be just as healthy a race if their attention were directed a little less to vitamins, pyorrhea, and St. George and the dragon, in the press and where the walls meet the ceilings of public conveyances. In its very nature, life is a series of risks. The risks should be parried with intelligence, but when the final one triumphs, it should be met as Socrates drank the hemlock.

Adequately to discuss mycosis fungoides, cutaneous leucemia, Hodgkin's disease and associated conditions will some day be the topic of a necessary monograph. The subject is too vast for this paper and were it not because the lesions of these diseases, in so far as the skin is involved, are tumors, I would not interpolate this all too inadequate thumbnail sketch. There is another, but very remote clinical tie between them and Kaposi's sarcoma. They all are characterized by intensely itching prodromal lesions resembling urticaria, erythema multiforme, and the psoriasiform group of dermatoses, as well as the eczemas, prurigo, and lichenifications. Whatever the earliest appearance of the lesions, they sooner or later become infiltrated, then small and then large tumors with characteristics of form and color too numerous to mention in so unpretentious an outline. There are alternating periods of activity and relative calm. Treatment with the roentgen ray modifies the course and frequently staves off the lethal issue for years. It is its similar response to the x-ray that justifies the suspicion of Kaposi's sarcoma being a remote member of the group.

Histologically, but within limits, the cutaneous lesions of these diseases are characteristic enough but the literature abounds

with instances of one clinical type going over into another. In all of them there finally is general glandular involvement, and, in mycosis, the commonest of the three, frequently visceral involvement. Add to this the blood picture and enlarged spleen in leucemia, the Dorothy Reede cells in the glands and skin lesions of Hodgkin's disease, and the absence of such findings in mycosis, and the salient elements in differentiating among the three syndromes have been mentioned. What the etiology of these conditions is remains to be discovered. That they are related is more than a reasonable conjecture. That their pathogenic drama will be found in further investigations in the reticular endothelium I do not doubt. But these are matters for the pathologist to clarify and for tomorrow to reveal.

A word or so as to diagnosis and treatment of skin tumors, and this essay will be ended. If the reader will turn to Table 1, he will note that there are over thirty kinds of skin tumors, indeed many more if all possible subvarieties are considered. In general they are fairly characteristic as to site, number, shape, color, consistency, and the like. Thus they are usually easily grouped and often easily recognized by anamnestic and gross objective features. Nevertheless, small, early, and borderline lesions can be identified with certainty only by the microscope. It is for this reason that I believe histologic examination is of the greatest importance in the diagnosis of skin tumors. The procedure is not always feasible since human beings are averse to excision of face lesions.

The excision of small or isolated lesions for study also becomes a therapeutic process. Tumors must be destroyed or removed. There is no other way of getting rid of them. Destruction is accomplished by means of chemical or physical agents. The physical agent of choice is the desiccation spark or the coagulation current. The selection will depend upon technical factors. The roentgen ray is of great value in treating mycosis fungoides, leucemia, and Hodgkin's disease of the skin, Kaposi's sarcoma, and as an adjuvant in treating melanoma and sarcoma. Radium in one of the many ways in which it may be employed is also useful, according to some, but my own enthusiasm for

it is scarcely more than tepid. This outline does not exhaust the subject and the precise treatment adopted for a particular case requires the experience and discrimination of an expert.

Prognosis is a matter I shall scarcely touch on. The majority of skin tumors can be satisfactorily gotten rid of. The various points involved are indicated in the body of this paper. Cosmetic as well as biological questions are involved and these depend entirely on the location and nature of the tumor. Therefore, prognosis becomes a matter of common sense. The prognostically grave skin tumors are melanoma and the metastatic and reticular endothelial growths, as well as Paget's disease, xeroderma pigmentosum and roentgen skin growths. All others are relatively or absolutely benign. Fortunately the last constitute the bulk of the total.

Skin tumors are an interesting and important branch of morbid biology. If their nature and cause were understood, the reflected light would probably illuminate kindred problems in other tissues. What is known best about them is how they act and how they look to the naked eye and under magnification. Any incrustation of theory not supported by fact is misleading. It is for this reason, and to restore the subject to clinicians in all its honest simplicity, that I have handled the theme as I have. The discussion of "precancerous" lesions took the form it did in this contribution in order to illustrate how obscurity can be rendered thrice obscure by meaningless verbiage. Human beings are precancerous as we know, for they get cancer. Where a cancer has developed, the tissue must have been precancerous, by the same token, whether it was previously apparently normal or not. But to call the previously abnormal area precancerous is an unwarranted assumption. An assumption remains an assumption until evidence crowns it as a fact. What predisposes to cancer is not known. There is nothing more today than hints of what does. When the word "precancerous" first reared its head, the tentativeness of actual knowledge perhaps justified the term. But the term scarcely held its own. So when it muscled in again with the alias of "supervensiveness in cancer," displaying all of its old triteness under the new soubriquet, it

seemed to me necessary to find out its real merit. Tables 4 and 5 amply illustrate this. In another decade, no doubt, history will repeat itself. May I suggest to the next votary at this somewhat artificial shrine that he try a phrase something like "cancer proclivity in skin lesions," just for the sake of novelty? It will take only one reading, of course, to reveal that it is the same old dog reawakened, but until he is again lulled to slumber the writer who woke him up will get a new hearing for himself and for all the other "precancerists" from Dubreuil on.

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POLYSEROSITIS (PICK'S SYNDROME) ASSOCIATED
WITH RHEUMATIC VALVULAR DISEASE WITHOUT
PERICARDITIS

IN the differential diagnosis of persistent or recurrent ascites with or without accumulations of fluid in other serous sacs, clinicians frequently consider the diagnosis of polyserositis. While older observers recorded cases exhibiting this syndrome, and Concato¹ in 1881 carefully described 2 cases of tuberculous inflammation of the serous sacs, it was Pick² who clearly showed one mode of its pathogenesis.

We may profitably note Pick's description in 1896. Curschmann³ in 1883 had described similar morphological changes and likened the change in the liver to an application of sugar-icing (Zuckergussleber).

Pick recognized that adhesive pericarditis, of variable etiology and with no reference to valvular disease, might initiate the syndrome. In two of his cases there was tuberculous pericarditis, and in one pericarditis was consequent to a pneumonic infection. He thought that interference with blood flow, with long-standing passive hyperemia in the portal system, was the most likely factor in the production of ascites. He also recognized the possibility that multiple paracenteses might set up low-grade chronic peritonitis to add to the factors producing ascites. But he considered long-standing congestion of the peritoneum of equal importance. He closed his description with

emphasis on the adherent pericardium as the seat of the primary effect.

The outstanding features of Pick's syndrome are generally held to be evidence of chronic adhesive pericarditis, involvement of the peritoneum and the capsule of the liver by chronic nonspecific inflammation of the serous surfaces with the chief clinical manifestation of marked recurrent or persistent ascites. Adhesive pleuritis may or may not be present; and capsular involvement of the spleen and extension of the serous surface inflammation over the other viscera may be present without recognizable signs or symptoms.

In a review of the literature of cases of polyserositis one recognizes the variable etiology which may result in a fully developed symptom complex sharing many of the features referred to by Pick. The symptoms of the disease necessarily vary according to the predominant serous sac involved. However, as a rule ascites is the most prominent feature.

It should be emphasized that the fully developed syndrome is rarely found in conditions which one would expect might lead to its clinical appearance. Thus, adherent pericardium is a fairly common postmortem finding; tuberculous involvement of the pleura, peritoneum, and pericardium is not rare; tricuspid stenosis is not unusual. Yet in the great majority of such cases, Pick's syndrome is only rarely encountered.

Here we are concerned with a case showing the characteristic capsular changes in association with valvular heart disease but *without* adhesive pericarditis. Huebschmann⁴ in 1912 reported such a case. He believed that in his case stenosis of the tricuspid valve was responsible for the initiation of the syndrome but was convinced that the multiple abdominal paracenteses had added a secondary chronic infection which contributed to the recurrence of ascites.

With renewed interest in this syndrome due to the introduction of effective surgical treatment of the pericardial lesions it seems worth while studying the following case which presented the essential features of the syndrome *without* adherent pericardium.

Case Report.—N. L., thirty-four-year-old Polish housewife, was first admitted to the Third (New York University) Medical Division of Bellevue Hospital, October 29, 1929, complaining of swelling of the abdomen.

Past History.—No history of rheumatic fever or chorea was elicited but she had had frequent sore throats for many years. Occasional stiffness of the joints of the fingers began several years before. In 1921 at the age of twenty-six a hysterectomy and salpingo-oophorectomy were performed. She insisted that the onset of her chief complaint followed this operation. She was at first troubled with dyspepsia and belching of gas, followed shortly by swelling of her feet and abdomen. The swelling would recede after taking drops (probably digitalis) and would reappear when she discontinued them. Dyspnea also appeared about this time and gradually became worse. Precordial pain began four years after the onset of the abdominal swelling. In August, 1929, two months before admission, the patient went to a hospital where an abdominal paracentesis was performed. At this hospital she remained about six weeks and shortly after discharge sought admission to Bellevue Hospital because of the rapid reaccumulation of fluid.

Physical Findings on Admission in 1929.—The patient was pale, dyspneic, orthopneic, and cyanotic. The veins of the neck were dilated and pulsated. The pupils were dilated, equal, and reacted to light. The conjunctivae were pale. No petechiae were seen. The sclerae were not icteric. The teeth were in very poor condition. Tonsils not visible. There was no clubbing of the fingers, nor were any nodes palpable. The lower extremities presented moderate edema. A moderate amount of ascites distended the abdomen. The liver was palpable 8 cm. below the right costal margin; not tender nor pulsating. The spleen was not palpable. The lungs presented diminished resonance at both bases with moist râles audible from the angle of the scapulae down.

Heart.—The point of maximum impulse was visible and palpable in the sixth intercostal space 12 cm. to the left of the midsternum, outside of the midclavicular line. The sounds at the apex and base were faint. The pulmonary second sound was slightly accentuated. A long, rumbling low-pitched diastolic murmur preceded by a short, harsh systolic blow was best heard over the apical area. A diastolic thrill was palpable at the apex. No murmurs or thrills were elicited at the base. No abnormal pulsations were visible. The rhythm of the heart was totally irregular, rate 94; pulse rate, 92; pulse deficit, 2. Blood pressure, 146/84. Temperature, 99.2 F.

Diagnosis.*—Cardiac: (a) *Etiologic*: Unknown (rheumatic?) inactive. (b) *Anatomical*: Enlarged heart, mitral stenosis and insufficiency. (c) *Physiologic*: Auricular fibrillation. (d) *Functional*: Class III (*i. e.*, signs of heart failure at rest).

Subsequent Course and Observations.—Despite complete digitalization to the point of mild toxicity, *i. e.*, slight nausea and headache, the liver remained palpable 8 cm. below the costal margin and the ascites was not diminished. The edema of the legs disappeared. The ventricular and pulse rates at this time were 56.

* Diagnosis conforms to the nomenclature for cardiac diagnosis recommended by the American Heart Association.

It was thought that the ascites might be due to low-grade rheumatic peritonitis. Other possibilities offered at this time were primary cirrhosis of the liver and so-called "cardiac cirrhosis."

By December the patient had lost 16 pounds following the use of novarsuroi and ammonium chloride begun November 23rd. She was neither dyspneic nor cyanotic but the marked pallor of the skin and mucous membranes remained. The liver had not diminished in size. The spleen was now palpable two fingers below the left costal margin.

Several blood cultures were sterile. Urine analysis was normal. Blood count showed the following: Red cells, 3,800,000; hemoglobin, 50 per cent; white cells, 6800; polynuclears, 74 per cent; lymphocytes, 22 per cent; transitorials, 3 per cent

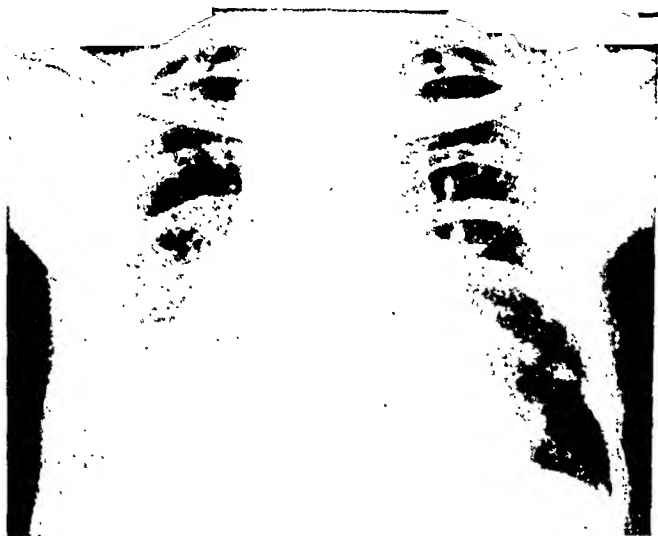


Fig. 33.—Teleoroentgenogram of the heart. Note enlargement in all diameters. The pulmonic fields show congestion and an interlobar plastic pleurisy in the right lung. The right costophrenic sinus is obliterated.

Roentgen examination of the chest on November 18th showed the heart to be enlarged in all diameters (Fig. 33). Both lungs showed increased density toward the hilus; the right costophrenic sinus was obliterated. An interlobar fissure on the right side was outlined by a dense linear shadow.

Several electrocardiograms showed auricular fibrillation, the rate ranging between 50 and 70. There was no deviation of the electrical axis.

On December 20th the patient was discharged improved from the hospital and referred to the Cardiac Clinic. The ascites had disappeared entirely. The liver, however, remained the same size as on admission. Within eight days (December 28th) the patient returned to the hospital because of swelling of her face, legs, and abdomen. A new complaint was weakness. The physical

findings were essentially the same as on the first admission except for edema of the face. The ventricular and pulse rates were slow, 70, and the rhythm wholly irregular. Ascites was again marked. The lower extremities were markedly edematous. The patient had gained 28 pounds since discharge on December 20th.

Calcium lactate was used in large doses but was discontinued after two weeks with no apparent improvement in the patient's condition and digitalis was then begun. The patient improved on digitalis and bed rest, losing considerable weight. A urine sediment count (Addis*) taken about this time gave the following results: (twelve hours) No albumin; red blood cells 20,960; white blood cells, 1,834,000; casts, none.

The blood pressure ranged from 108/60 to 146/84; average about 120/65. The temperature ranged between 98.6 F. and 101.6 F.; average 100 F.

On January 26th theocin was begun, and on leaving the hospital on February 2, 1930, the patient's weight was again down to 112 pounds. Although she had some signs of congestive failure she was considerably improved.

Observations Before Death.—The patient was readmitted on February 13, 1931, one year later, and died after five days. After leaving the hospital a year ago she had attended the clinic of another hospital and was admitted to the hospital many times for abdominal paracenteses. The last tap, which was the 22d, was performed ten days prior to admission but the abdomen again became tremendously distended, and the patient entered the hospital.

The patient was in marked congestive heart failure with massive ascites and edema of the abdominal wall. The liver was palpable but its lower margin could not be defined because of the unusual distention of the abdomen.

Digitalis was begun the following day. Because of the marked respiratory embarrassment abdominal paracentesis was performed and 8.5 liters of clear, light yellow fluid were removed. Although the patient felt relieved there was no improvement in her general condition. Ascites began to reform almost immediately. The following day she became delirious. Pulmonary edema set in and on February 18th she died.

Laboratory Data.—Urine, cloudy, amber; specific gravity, 1005; acid, no glucose, moderate albumin, and 30 white blood cells per high power field. A blood count showed red blood cells, 3,390,000; hemoglobin, 70 per cent; white blood cells, 4400; polynuclears, 87 per cent; lymphocytes, 12 per cent; eosinophiles, 1 per cent.

An electrocardiogram showed auricular fibrillation but the voltage was low in contrast to that of the tracings of previous admission. There was no deviation of electrical axis. Temperature ranged between 97 F. and 100.4 F. Blood pressure was 104/80 on admission and fell to 78/54 on day of death.

Final Diagnosis.—Cardiac: (a) Unknown (rheumatic?), inactive. (b) Enlarged heart with mitral stenosis and insufficiency. (c) Auricular fibrillation. (d) Class III.

The Significant Pathologic Findings Were as Follows.—(Necropsy No. 16513.) There was diastasis of the rectus abdomini muscles. The abdomen

* Normal values for twelve-hour specimens should not exceed: red blood cells, 500,000; white blood cells, 1,000,000; casts up to 5000.

binding them to the pleural aspect of the diaphragm on both sides. This layer was thick, opaque, and firmly attached to the inferior aspect of both lungs, although more extensively on the right side. The diaphragm musculature was thinner than normal and in places the muscle bundles were widely separated. The diaphragm was at the level of the fourth rib on both sides. Its inferior aspect showed a hyaline, opaque, white thickening which was confluent with the liver. The inferior vena cava measured 2.5 cm. in diameter in its intradiaphragmatic portion and was not dilated above or below this



Fig. 36.—A view of the superior aspect of the liver showing the irregular "sugar-icing" of the capsule. A represents the opening of the inferior vena cava surrounded by the thickened diaphragm.

level. Both lungs were small and crepitant throughout. On section, moderate congestion was seen in both lower lobes.

Peritoneum.—There was a diffuse thickening, "sugar-icing," of the peritoneum covering the abdominal viscera particularly in the upper half and lining the anterior abdominal wall to the suprapubic level. The peritoneal cavity contained about 4 liters of amber fluid in which a few flakes of fibrin were found.

Liver.—Appeared reduced in size. Capsule was strikingly thickened. It retained its glistening surface. The normal brown color of the underlying parenchyma was visible in only a few places. The "sugar-icing" was applied

irregularly and in places small shallow areas were seen from 5 to 10 mm. in diameter through which the liver parenchyma was discernible (Fig. 36). The capsular fibrosis extended inferiorly over the gallbladder and completely buried it. On section the process was fairly sharply limited to the capsule. Small fibrous bands could be seen at the periphery of the liver extending into the parenchyma for a distance of 3 or 4 mm. The cut surface in the deeper portion showed the characteristic markings of advanced chronic passive hyperemia, giving a well-marked "nutmeg" appearance. The gallbladder and bile ducts, when opened, were normal.

Spleen.—The organ was small. Its capsule showed a similar "sugar-icing" effect due to the marked thickening of the capsule (Fig. 37). It also



Fig. 37.—A view of the spleen and pancreas showing their thickened pearly-gray capsules. Note that the lesion is sharply limited to the splenic capsule.

retained its smooth surface. On section the markings were plain. The pulp appeared cyanotic and was quite firm.

Esophagus, Stomach, Intestines.—Esophagus was natural throughout. Stomach showed marked thickening of the serosa, similar to that seen over the spleen and liver. A few focal mucosal hemorrhages were seen when the stomach was opened. The intestines were natural except for a few adhesions between a few adjacent loops. No adhesions were found in the pelvic portion of the peritoneal cavity.

Pancreas.—Upon exposing the pancreas the peritoneum covering it appeared as a thickened pearly-gray capsule (Fig. 37). The parenchyma on section was natural.

Kidneys.—Normal in size. The capsule stripped readily leaving a smooth surface. On section the markings were plain. The opened pelves, ureters, and bladder were normal.

Genitalia.—Operative removal of the uterus, cervical stump being completely buried in adhesions. The ovaries were not found.

Microscopical Report.—*Heart and Great Vessels.*—Sections of the epicardium show no inflammatory changes. The myocardium of the ventricles is noticeably free from scars or other inflammatory changes. Sections of the auricles present marked fiber hypertrophy with corresponding increase in the size

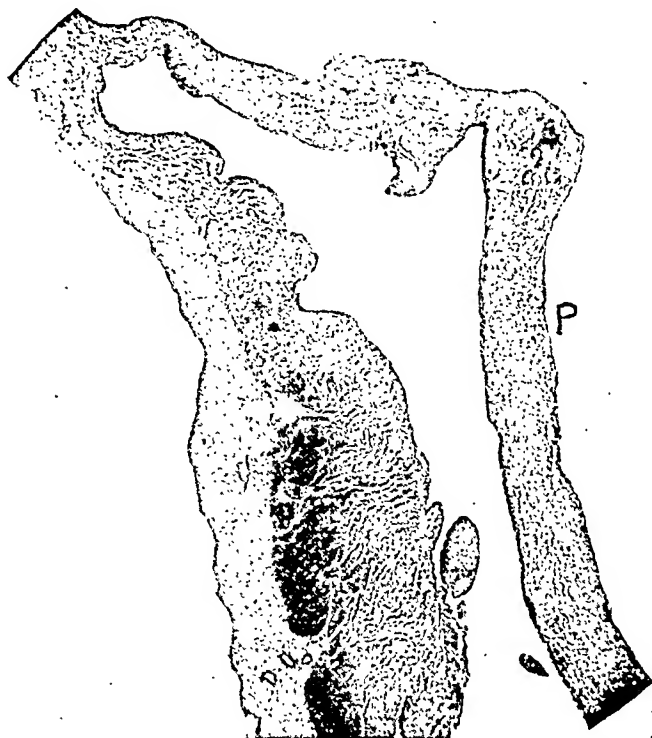


Fig. 38.—A low-power microphotograph ($\times 10$) of a section through a leaflet of the tricuspid valve including the elongated, hypertrophied papillary muscle (indicated by *P*). Note the short and thickened leaflet and the well-preserved ventricular myocardium. The loose fibro-fatty structure of the epicardium is intact.

of the nuclei. The sections of the right auricular appendage show the mural thrombus to be well organized at its base. The sections through the papillary muscles of both ventricles disclose advanced scarring which is both interstitial and intrafascicular. Sections of the tricuspid valve exhibit marked sclerosis and hyalinization which involve the distal portion of the valve leaflet much more than the proximal (Fig. 38). Blood vessels are numerous but

there are no signs of active interstitial valvulitis. The only evidence of fresh involvement is the finding of well-formed verrucae on the line of closure; these are composed of fibrin, proliferated histiocytes and fibroblasts. In the base of the valve the nutrient arterioles show moderate sclerosis of the wall but no acute changes are seen in the vessels.

Sections of the mitral valve disclose advanced sclerotic and hyalin changes with vascularization but no evidence of fresh valvulitis. .

The endocardium of the auricles is thickened. The elastic layers are somewhat broadened but no lesions of active endocarditis are found. The coronary vessels appear natural throughout. The sections of the aortic and



Fig. 39.—A low-power microphotograph of a section of the liver. Note the thickened hyalinized capsule. Only a few radiating bands of fibrous tissue can be faintly seen extending into the congested parenchyma for a few millimeters.

pulmonic valves reveal no changes. Sections of the aorta and pulmonary artery likewise reveal no changes.

Lungs.—Sections of the lung show evidence of chronic passive hyperemia with increased tortuosity of the pulmonary capillaries and many heart failure cells within the alveoli. The pleura is somewhat thickened in places due to the deposition of small amounts of connective tissue. Sections from the base of the lung through the adhesions to the diaphragm present marked sclerosis and thickening of the visceral pleura.

Diaphragm.—Both aspects of the diaphragm show marked thickening of the peritoneal and pleural reflections which is more marked on the pleural side in some places and on the peritoneal side in others. Many of the sections simply show many layers of partially hyalinized connective tissue in which

very few cells are encountered. Several sections, however, show infiltration by new blood vessels and small foci of lymphocytes and histiocytes. The blood vessels themselves show no inflammatory changes, recent or old. Where the muscle of the diaphragm is intact the only change noted is an occasional focus of Zenker's hyaline degeneration.

Liver.—Sections of the liver which include the capsule show Glisson's capsule to be thickened many times by the deposits of hyalinized connective tissue (Fig. 39). In places bands of fibrous tissue are seen to extend from the capsule into the adjacent parenchyma for a comparatively short distance.

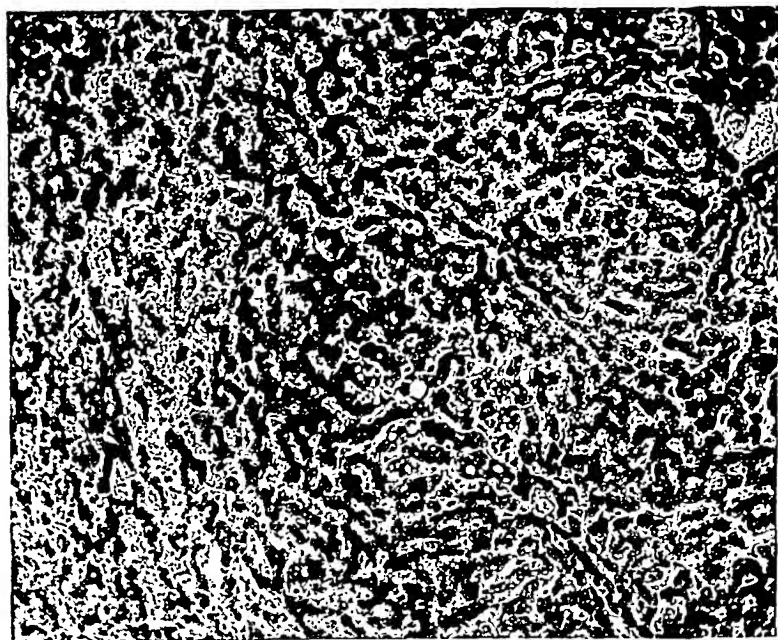


Fig. 40.—A low-power microphotograph of section of the liver showing dilated sinusoids, particularly marked at one side. The parenchyma is fairly well preserved except where the chords are atrophic.

The blood vessels near the capsule show moderate uniform sclerosis with diminution in the size of the lumen but no changes which can be considered inflammatory. The parenchyma throughout reveals a uniform picture of advanced chronic passive hyperemia (Fig. 40). The sinusoids are widely dilated and crowded with erythrocytes as are the central veins. In the central portions of some of the lobules necrotic liver cells can be made out. The intact cords of liver cells are narrow and atrophied. Small amounts of golden pigment are seen within some of the liver cells and in the sinusoids, particularly in the cells of Kupffer. The portal areas show no notable changes.

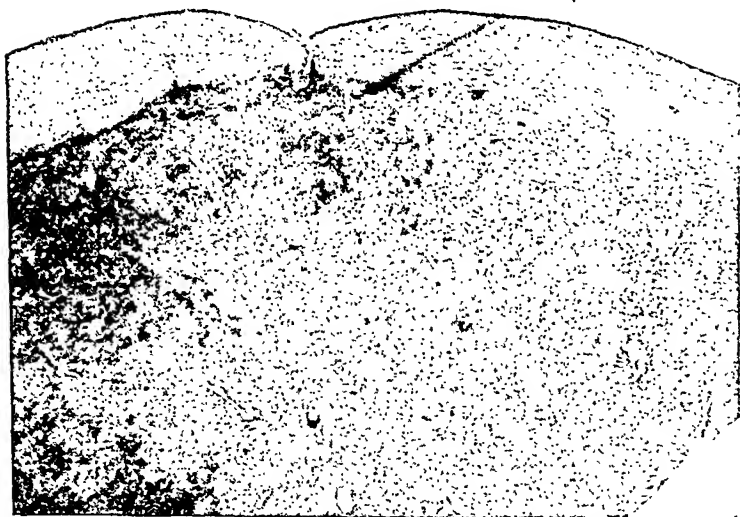


Fig. 41.—A low-power microphotograph of a section of the spleen to show the capsular fibrosis.



Fig. 42.—A low-power microphotograph of a section of the pancreas showing the moderate thickening of the retroperitoneal capsule.

Sections through the wall of the stomach and gallbladder confirm the gross diagnosis of serositis. The mucosae of these viscera manifest no changes.

Spleen.—Sections of the spleen (Fig. 41) likewise exhibit the deposits of large amounts of connective tissue which has undergone hyalinization on the

capsule. No foci of cellular infiltration are found. The underlying splenic pulp shows increased pigment deposit, marked congestion of the sinusoids with fairly well-preserved malpighian bodies. The arterioles show moderate sclerosis.

Pancreas.—The parenchyma appears rather well-preserved while the overlying peritoneum is moderately thickened (Fig. 42) due to the deposit of moderate amounts of cellular connective tissue.

Sections of the other organs confirm the gross diagnosis.

Final Pathologic Diagnosis.—Polyserositis, pericardial effusion, chronic adhesive pleuritis, chronic peritonitis with ascites, chronic perihepatitis, chronic perisplenitis, chronic perigastritis, chronic peripancreatitis, chronic pericholecystitis. Heart: Hypertrophy and dilatation of the auricles, advanced tricuspid and mitral stenosis, verrucous endocarditis of the tricuspid valve, mural thrombus of right auricular appendage, ball-valve thrombus of the left auricle. Lungs: Pulmonary congestion (right), healed peribronchial lymphatic tuberculosis. Liver and Spleen: Passive hyperemia. Operative removal of uterus, tubes, and ovaries.

Comment.—Although frank rheumatic manifestations in life were few, the valvular lesions and occasional myocardial scars found at autopsy leave little room for doubt as to the rheumatic etiology.

The pathologic physiology involved in the development of the Pick syndrome in our patient is complex. There are several possible factors or related alterations. First, swelling of the abdomen associated with dyspnea was first noted, eight years before admission, following a laparotomy for gynecological disease. Whatever rôle the peritoneal irritation or inflammation at the time of operation played in the subsequent course of events was not great but should not be entirely ignored. Certainly relief of symptoms (whether they were due to congestive heart failure or polyserositis) was obtained by the use of medication (digitalis?) and rest for the next eight years.

A second possibility to be considered is a more specific inflammatory process of the serous sacs, namely rheumatic infection. Reports of polyserositis during the course of rheumatic polyarthritis are not unknown. Recently Paul⁵ has recorded a well-studied case of rheumatic fever with carditis and lesions considered specific for rheumatic fever, located in the diaphragm and the peritoneum, representing what might be termed a perihepatitis and perisplenitis. Lenoble and Pineau⁶

have also reported a fatal case of rheumatic fever in which pericarditis and perihepatitis were found at autopsy.

While we have found no evidence in our histologic studies of the diaphragm or liver or spleen to indicate the presence of old or recent rheumatic vascular or perivascular lesions it may be that we are dealing with the end-stage of such a process in which identifiable lesions may not be found. However, Volhard⁷ apparently did not consider or recognize inflammation as an etiologic factor in so far as he held that the "Zuckergussleber" was the result of the chronic ascites rather than the cause.

In this case it should be stressed that our studies of the serous sacs of the various organs involved revealed no underlying inflammatory change which could account for the deposition of the prominent, thickened membrane. It is possible that it was the result of an inflammatory exudate but there is the possibility that such laminated deposits over the viscera may be the result of another factor, namely, the rubbing and pressing action of the viscera during active peristalsis, and the action of the diaphragm on the liver and spleen. We have seen such membranes in cases not exhibiting the Pick's syndrome in life and most often over the superior aspect of the liver and spleen. Such an explanation is based upon the assumption that in polyserositis we are dealing with an exudate rich in fibrin or fibrinogen.

It has been shown experimentally^{8, 9} that in adhesive pericarditis high-grade stasis in the liver may be due to constriction of the inferior vena cava. Recently the experimental¹⁰ production of ascites in dogs by partial ligation of the inferior vena cava between the heart and the diaphragm has been reported. Beck and Griswold¹¹ in this country have produced the Pick syndrome in dogs by both intrapericardial and extrapericardial adhesions. While no intrapericardial adhesions were present in our case, there were found pleuropericardial adhesions and the diaphragm was greatly scarred and thickened particularly over the liver and around the inferior vena cava. The inferior vena cava was not constricted (it measured 2.5 cm. in diameter in its entire diaphragmatic portion) nor was the opening into the right auricle encroached upon.

The manifest tricuspid stenosis, advanced mitral stenosis, and auricular fibrillation (all factors of long standing) seem sufficient to interfere with the normal cardiodynamics, particularly with diastolic filling. The subsequent high-grade portal stasis and ascites, associated with the en masse constriction of the liver by a universal pericapsular fibrosis, readily account for the development of the syndrome. The rarity of the syndrome in association with tricuspid stenosis suggests that other factors play a rôle in the development of the syndrome. Serositis may be one factor and loss of distensibility of the liver due to capsular fibrosis may be another.

An additional point is worth consideration. Since the introduction of surgical procedures for the relief of adhesive or constrictive pericarditis and the Pick syndrome, the diagnosis of adherent pericardium in suspected cases is apt to be made. Signs, as Sprague and White,¹² and Beck and Griswold¹¹ have emphasized, are often obscure and the diagnosis is difficult. The observations recorded in this case emphasize the necessity for accurate differential diagnosis before subjecting such patients to surgery of the pericardium.

Summary.—Pick's syndrome may appear under the following circumstances: first, in constrictive lesions, of variable etiology, about the heart which interfere with filling of the right heart; second, chronic valvular disease (tricuspid stenosis) with congestive failure and polyserositis (rheumatic?). In these two groups portal stasis may be held accountable for the development of ascites while polyserositis may supplement this factor; third, active specific infections of the serous sacs (tuberculosis and rheumatic fever).

We feel that congestive heart failure in association with advanced tricuspid and mitral valvular disease and auricular fibrillation was the underlying cause of the symptoms in the case discussed.

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NONTROPICAL SPRUE

IN 1766 Hillary,¹ writing of the diseases endemic in Barbadoes, described a condition which he had encountered and to which he gave the name *aphthoides chronica* or *impetigo primarum viarum*. The clinical picture as he presented it is indistinguishable from sprue. While there are occasional accounts² from the Far East and from India of conditions somewhat similar, it was not until the publication of the extensive papers of Manson³ and van der Burg⁴ that sprue was recognized as a distinct and separate disease. It has since become well known, especially in the field of tropical medicine, and has been considered to have a well-defined geographic distribution largely restricted to China, the Philippines, the Dutch East Indies, Ceylon, northern Australia, India, and in the Western Hemisphere the island of Porto Rico. It is excessively rare on the continent of Africa.⁵

Sprue is a symptom complex, well-defined and unmistakable in the characteristic advanced case but presenting many modifications which may confuse and obscure the clinical diagnosis. There may be great variety in the combination of the symptoms, in their severity and in the rate of progress of the disease. It usually begins insidiously, runs a chronic or remittent course, and when apparently cured tends to relapse in acute form. There is a striking uniformity in the history of most cases. Sooner or later after entering the endemic region an irregularity of the bowels develops which may persist for months or years without particularly disturbing the general health or comfort.

This commonly takes the form of an early morning diarrhea with two or three liquid or soft stools before breakfast and no further evacuation until the following morning. Gradually involvement of the buccal and lingual mucous membrane occurs varying from time to time in intensity and duration. Crops of minute vesicles appear on the tip or sides of the tongue, the frenum, or the inner aspect of the lips, and subsequently burst leaving the superficial, acutely inflamed, characteristic aphthous ulcer. These may be extremely painful, at times to such a degree as materially to impair the ability to take food, and leading the patient to choose semistarvation rather than to undergo the discomfort of eating. With the exacerbations of the mouth condition the character of the diarrhea changes. The stools increase in number and are no longer restricted to the early morning hours. They gradually become pale in color, more bulky than normal, frothy, acid in reaction, and foul. Coincidentally other digestive symptoms appear. Distention, at first epigastric and associated with belching, becomes general. While pain is uncommon a sense of epigastric discomfort after meals is usual. Eructations of sour bitter fluid and, occasionally, vomiting occur. The periods of active symptoms become more frequent and of longer duration. An already delicate digestion becomes even more sensitive and acute exacerbations promptly follow upon slight dietary indiscretions. Ultimately deterioration of general health occurs with wasting, lassitude, and weakness, gradually leading up to complete invalidism. The loss of weight and diarrhea continue, the latter becoming constant and the stools typically gray or white and frothy. The skin assumes a grayish earthy tinge with brownish pigmentation over the temples, the malar region, the rami of the jaw, the lateral aspects of the neck below the mastoid processes, the axillae, and over the inner aspect of the thighs. It becomes dry and scaling, and loses the normal elasticity. The tongue, previously the site of aphthae and swelling and inflammation of the papillae, undergoes a varying degree of smooth atrophy often accompanied by extensive fissuring. Appetite becomes very variable. During periods of increase, indulgence commonly results in increased severity of the diarrhea. Anemia

develops which may become severe. Ultimately the emaciation and cachexia become profound, edema of the extremities appears and death occurs as the result of inanition or intercurrent disease.

Much of the pathology of sprue is controversial. There is a great reduction, if not complete absence, of the subcutaneous, retroperitoneal, and epicardial fat. The tongue is often wasted, glazed, atrophic, and devoid of papillae especially the distal portion. The liver is considerably reduced in size and the heart is frequently below normal weight. The lungs, spleen, pancreas, and kidneys show no significant alterations. The changes described in the stomach and intestinal tract, however, have varied within wide limits. The earlier writers described the lesions as essentially a chronic progressive subacute inflammation of definite type followed by round cell infiltration and an atrophic fibrosis producing the thinned diaphanous wall so commonly described.^{6, 7} More recently the essential lesion has been considered to be an atrophic enteritis, but the initial inflammatory changes are said to be patchy in distribution, transient in duration, and not always evident at autopsy.⁸ The spinal cord does not appear to be affected.⁹ The decrease in size of the liver, which is stressed as one of the important physical signs and differential diagnostic features of sprue, is to be regarded not so much as a specific atrophy, but as an effect of chronic starvation in which depletion of the glycogen stores consequent on deficient carbohydrate intake plays an important rôle.¹⁰ More recent studies indicate that the changes encountered in the intestinal tract such as degeneration and desquamation of the epithelium, together with the atrophy of the wall, emphasized by the earlier writers as characteristic of sprue, are to be regarded as post-mortem changes, and that there is no characteristic underlying pathology.¹¹

Similarly reports of the condition of the bone marrow are at variance. In the early studies no abnormalities were noted.⁷ With further examinations limited to the femoral and tibial marrow three types of change were noted, most commonly an aplasia or hypoplasia, less often a moderate or marked hyperplasia, and the replacement of the normal yellow fat of the

medullary cavity by a greenish or light yellow gelatinous material. In the areas showing hyperplasia there is evidence of marked proliferation, with numerous myelocytes, and large numbers of megaloblasts and normoblasts. The picture as a whole is indistinguishable from that seen in pernicious anemia. In the more usual aplastic or hypoplastic type, however, the gelatinous substance consists almost entirely of fat. A few nests of mature erythrocytes are seen, nucleated forms are scanty and the majority of these are normoblasts.¹⁰ The sternal marrow, on the contrary, seems uniformly to undergo a megaloblastic change comparable to that of Addisonian anemia and to present no evidence of aplasia.¹²

The character of the stools in sprue presents one of the outstanding features of the disease. The light color of the fecal matter was at first associated with the progressive diminution in size of the liver, and attributed to diminished or absent secretion of bile consequent upon physiologic failure of the organ. It was found later that the bile is normally secreted but that hydrobilirubin, which imparts the normal brown color, is reduced to the colorless form leuko-urobilin.⁷ The greatly increased bulk of the dejecta is due to the excessive amount of fat present, which may constitute from 25 to 48 per cent or more of the dried weight of the feces.^{13, 14} This has been split normally with fatty acids in excess of neutral fat indicating a faulty absorption rather than a failure of digestion, which has been advanced as a factor in the disease. The ratio of unsaponified-saponified fat, and examination for the presence of pancreatic ferments point to a normal external secretion of this organ.¹⁵

In most instances the ability of the gastric mucosa to secrete hydrochloric acid under the stimulus of the simple test meal, alcohol, or histamine is retained, although there is commonly a hypochlorhydria.⁸ In the cases presenting an apparent achylia gastrica clinical recovery may be associated with restoration of this function.

Blood chemistry determinations indicate certain characteristic changes. The calcium values are usually slightly below normal, and the inorganic phosphorus normal or somewhat

reduced. The plasma cholesterol content is reduced. Serum bilirubin may be increased in amount but rarely to the extent encountered in pernicious anemia during an exacerbation. High indirect van den Bergh reactions are exceptional in sprue. Glucose tolerance test shows a low blood sugar curve.

The not infrequent occurrence of tetany during the active phase of the disease, and the commonly encountered low blood calcium without tetany, have been attributed to disturbed function of the parathyroid glands,^{16, 17, 18} and to faulty absorption from the intestinal tract. The weight of evidence points to the latter. It is probable that all the calcium in the food is altered by the processes of digestion to the inorganic form and absorbed as partially or completely ionized salts. Whether soluble or insoluble these appear to be absorbed with difficulty and their passage through the intestinal membrane seems to be largely effected by vitamin D.¹⁹

The anemia of sprue was long considered to be of the secondary type despite the frequent presence of a high color index and morphological changes suggesting the picture of pernicious anemia. Early observers noted that there is little change in the blood in the initial stages of the disease, but as it progresses a fall in hemoglobin and erythrocytes occurs with a lowered index. In more severe cases, and especially in the later stages many of the characteristics of the addisonian blood picture were recognized.^{6, 7, 20} With the increased knowledge of hematology in recent years these observations have been confirmed although the interpretations have changed.

In its earliest phases the anemia is of the simple hypochromic type subsequently becoming hyperchromic and megalocytic.²¹⁻²³ In the majority of instances the color index is unity or above at the time the patient first comes under observation, and may vary from time to time in the same individual.^{14, 15} Generally speaking patients with values of unity or above are more seriously ill than those with lower values.

The erythrocyte count is seldom reduced to the levels commonly found in pernicious anemia when the patient first seeks medical advice, although extremely low figures have been re-

ported. A large series of cases studied in Bombay and London averaged 3,200,000 red cells, hemoglobin 64 per cent, and the color index 1.⁸ The outstanding feature of the stained film is the marked anisocytosis with excess of megalocytes, and microcytes much less in evidence. Poikilocytosis and polychromatophilia may occur but are seldom as striking as in addisonian anemia. Punctate basophilia, normoblasts, and even megaloblasts may be present in severe cases but are less frequent than in pernicious anemia of similar intensity. The blood picture of sprue is essentially that of a megalocytic anemia with minimal signs of regeneration.

Price-Jones curves show the average diameter of the cells to be considerably above normal and the curve definitely displaced to the right. As a rule the curves are very asymmetrical, the bases broadened, the widening extending invariably to the right and in some instances to the left as well. Clinical improvement is accompanied by a progressive decrease in the average diameter of the erythrocytes and a corresponding shift of the curve to the left. Marked leukopenia commonly occurs only in the more severe grades of anemia. There is a slight increase in the number of lymphocytes at the expense of the neutrophil polymorphonuclear leukocytes.

In the advanced and terminal stages of sprue a condition simulating aplastic anemia may be encountered.²⁸ Discussing this complication Fairley²¹ says: "A crisis may be defined as the turning point in a disease indicating recovery or death, and, used in this sense, blood crises in sprue are not infrequently met with in the tropics. In certain of our cases, we have observed a rapid and critical fall in the hemoglobin and red blood corpuscles associated with severe diarrhea and progressing to a fatal issue without any evidence in the peripheral blood, either of hemolysis or of regenerative efforts on the part of the bone marrow. In this respect, the blood crisis in sprue is the reverse of the blast crisis in pernicious anemia where megaloblasts and normoblasts are usually in evidence, and polychromatophilia and anisocytosis constitute marked characteristics of the blood smears. Furthermore, in sprue a blood crisis is invariably a

terminal event, whereas it not infrequently heralds a definite remission in pernicious anemia."

There have been many theories concerning the etiology of sprue. Kohlbrugge (1901) found great quantities of yeast cells resembling *Monilia albicans* in the intestinal mucus, the lymphoid patches of the intestine, and in the epithelium of the tongue and esophagus. He recovered similar organisms, however, from the stools of patients suffering from other conditions. Subsequently Bahr (1912-1914),⁷ in Ceylon, and Castellani and Low (1913)²⁶ in London recovered fungi from the mouth or stools but did not consider the evidence sufficient to justify their acceptance as the cause of the disease. Ashford²⁷ in 1915 recovered a monilia which he considered previously unrecognized and to which he gave the name *M. psilosis* (Ashford). Further investigations revealing a very high incidence of infection with this organism in cases of sprue, and the presence of a positive complement fixation test with *M. psilosis* as antigen^{28, 29} led him to advance the theory that this infection was the cause of the disease. In 1922 he modified his concept of the etiology postulating an unbalanced dietary, at times producing a deficiency syndrome, which acts as a predisposing cause, permitting *M. psilosis* to gain a foothold. His observations have not had general confirmation. A fungus fulfilling the morphological and cultural requirements has been recovered frequently in the absence of active or past sprue. Fairley and Mackie (1916)¹⁴ summarize their own experience, and incidentally that of others, as follows: "In epitomizing our views on the significance of *M. ashfordi* in sprue the possibility of the yeast flora of the intestine multiplying more vigorously under conditions of decreased alkalinity in the small intestine with excessive production of acid and gas is recognized. Evidence, however, that any yeast plays a specific rôle in the etiology of this disease or that sprue is to be regarded as a moniliasis of the digestive tract is definitely lacking. We have never found systemic involvement of the tissues nor demonstrated *M. ashfordi* in pathologic lesions in the tongue or intestine of cases coming to autopsy. Furthermore, the distribution of *M. ashfordi* in human excreta in the

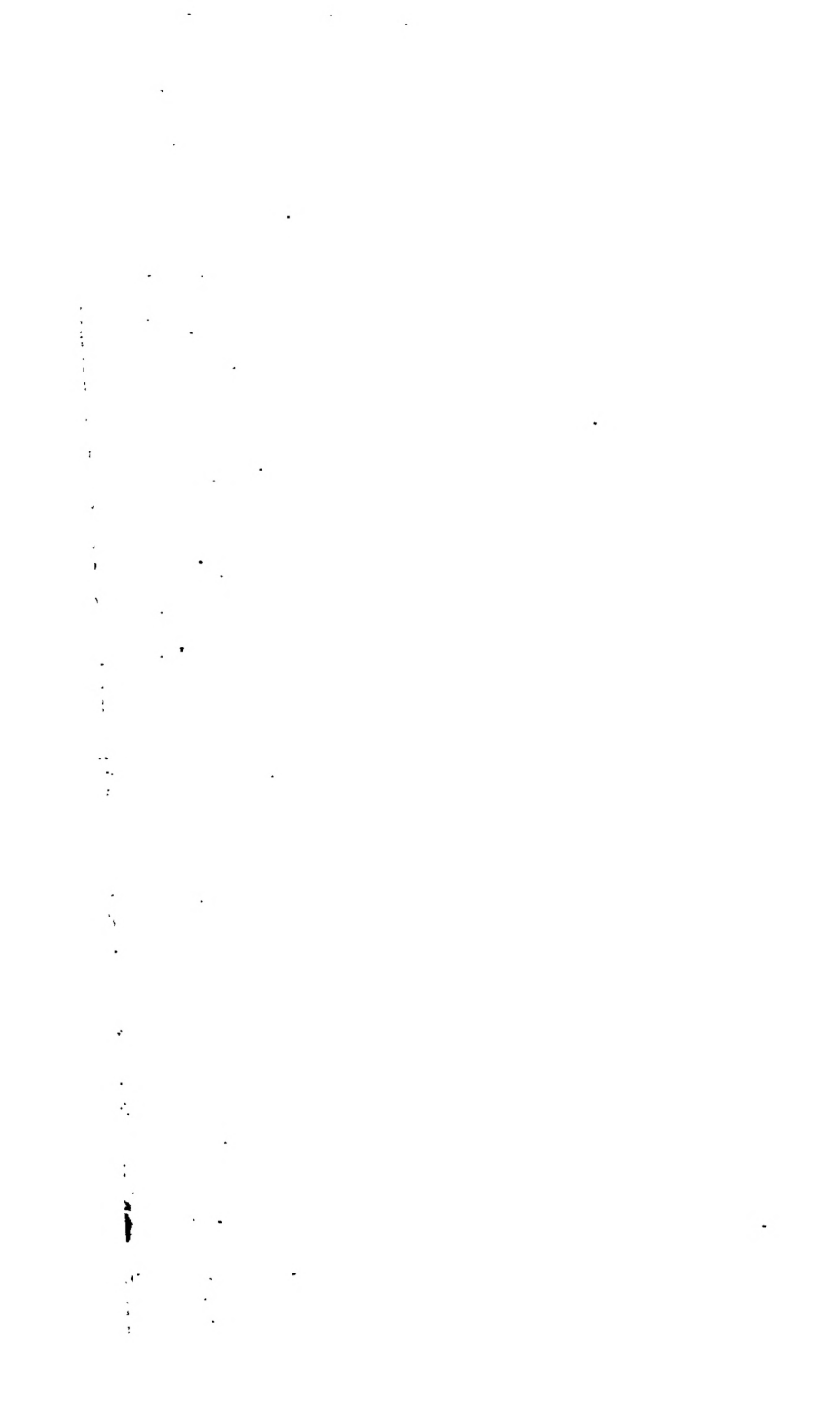
Bombay series has been so widespread that its presence in sprue feces becomes a matter of doubtful significance. The most that can be said regarding *M. ashfordi* is that, during the phases of the disease in which its increased biological activity can be demonstrated, it may be regarded as a contributory or secondary factor in the production of such intestinal features as abdominal distention, flatulence, and acid frothy stools, but never as the primary cause of the disease."

Both bacillary and amebic dysentery are frequent precursors of sprue in endemic regions and together with the streptococci and others of the intestinal bacteria, have been advanced from time to time as possible factors in the etiology.³⁰

The frequent association of a lowered level of the blood calcium, and the occasional occurrence of tetany, together with the clinical improvement observed after combined parathyroid extract and calcium therapy, led Scott (1923)³¹ to advance the hypothesis that the disease represented a disturbance in the regulatory function of the parathyroid glands.

More recent investigations into the etiology have led away from the concepts of infection and of the endocrine background. The possibility that sprue is a deficiency disease depending upon an avitaminosis and lack of adequate protein was suggested by Elders in 1917.³² Two years later McCarrison noted a condition developing in monkeys on deficient diets which somewhat resembled sprue in man.³³ Following Castle's demonstration of the rôle of the intrinsic gastric factor in pernicious anemia,³⁴ Castle and Rhoads¹² studied a group of 100 cases in all stages of the disease. They found a close relationship to pernicious anemia both as regards etiology and the most satisfactory methods of treatment and demonstrated in certain instances, in both the early and late stages of the disease, lack of extrinsic factor in the diet or of intrinsic factor in the gastric juice. In some of the advanced cases an apparent difficulty in the absorption of the hematopoietic factor from the intestine constituted an additional factor conditioning the major deficiency.

Within recent years the restricted distribution and the concept of sprue as a purely tropical disease have been challenged.



case presenting the clinical picture, certain of the complications, and illustrating well some of the difficulties of treatment.

Case Report.—The patient is a forty-three-year-old American woman who has always lived in New Jersey, except for a two weeks visit in Florida nine years ago and a brief West India cruise in 1928 touching at Jamaica and Panama. Her best weight was 118 pounds. She has had no serious illnesses but has noticed for many years that excessive fatigue or nervous strain would be followed by indigestion or diarrhea which was controlled by restriction of roughage in the diet. Moderately severe anemia has been present for at least ten years. About eight years ago recurrent bouts of afebrile diarrhea of two or three days duration began, attended by moderate exhaustion. In the last three years the stools during attacks were foamy, gray, greasy, and foul, accompanied by much flatus but without marked increase in bulk. The free intervals gradually became less frequent and the stools less normal at these times. Within the last year the exacerbations have been associated with moderate "heart burn," diminished secretion of saliva, and marked distention. The diarrhea became matutinal with several fairly characteristic stools between 1 o'clock and 5 o'clock in the morning with relative freedom during the remainder of the day. In December, 1931, her weight was 115 pounds but she shortly began rapidly to go down hill. Abdominal pain occurred with an unusually severe attack of diarrhea accompanied by nausea and vomiting. The stools remained continuously abnormal, anorexia set in, paresthesias of the hands and feet appeared, progressive weight loss occurred, and in the spring of 1932 the tongue became sore, and sore spots developed on the mucous membrane of the cheeks, and rhagades at the angle of the mouth. *Endamoeba histolytica* were found in the stools in May and she was treated by small doses of emetin by hypodermic and anayodin (iodoxyquinolin sulphonic acid). Following this a high protein diet and liver extract brought about a general improvement with gain in weight and formed stools. In July, however, pale, frothy, early morning diarrhea recurred. Anorexia, weight loss, asthenia, and finally marked palpitation and moderate edema of the extremities developed, but without tongue or mouth symptoms.

Detailed data are available concerning the anemia and other objective studies over the last ten years. An obviously severe grade of anemia was present in 1922 which was described as a secondary type. In the following year although the color index was 1.0 the morphology was considered normal. A gastro-intestinal x-ray examination in 1926 showed delay at the duodeno-jejunal junction and in the jejunum. The ileum was definitely dilated and contained barium at six hours. The liver was not enlarged and there was no evidence of gallbladder pathology. There was undue delay in the passage of the opaque meal through various portions of the small intestine without definite obstruction. At twenty-four hours the meal was scattered throughout the entire large intestine which appeared spastic in some portions, especially in the transverse colon. After forty-eight hours the barium was distributed throughout the colon although it was less dense than at the twenty-four-hour examination. A distinct cecal residue was present.

There is a gradually increasing number of reports of cases occurring in individuals who have never visited the endemic areas. The majority of them are from the southern United States, a scattering from the northern and central portions, and isolated instances in Denmark, Holland, Germany, and England.

The first accounts of nontropical sprue are those of Graham³⁶ and Harris,³⁶ 1905 and 1907, who reported its occurrence in Georgia. Some 70 cases have now been recorded (Table 1). However, it is doubtful if all of these can be accepted as sprue. Thirty-six of the cases are presented without clinical data. Five more are quite atypical, and another must be excluded because duodenal obstruction secondary to a large duodenal ulcer preceded the development of the clinical picture. There remain, then, 28 cases which seem to be unquestioned instances of the disease.

The differential diagnosis especially in the southern United States may be excessively difficult because of the frequent occurrence of pellagra. An undeveloped case of either condition may easily be mistaken for the other. Both are insidious in onset, chronic, and prone to recur. Gastro-intestinal symptoms are in the foreground of both pictures and gastric hydrochloric acid may be present or absent in either. In sprue, however, the tolerance for fat and carbohydrate is notably diminished and there is a much greater tendency to severe anemia, while the sensitivity of the skin to sunlight, and the lesions of the brain and cord so constant in advanced pellagra are extremely rare if they occur at all in sprue.³⁷ There is no one trustworthy microscopical or laboratory test which is characteristic of sprue alone. It is a symptom complex which may be mimicked closely by abdominal tuberculosis, pancreatitis, and pernicious anemia. Gastrojejunal colic fistula may produce a condition indistinguishable from typical sprue.³⁸ Manson-Bahr³⁹ has said that before accepting a case as true sprue originating in England he would expect to see not only the typical diarrhea, flatulency, anemia, tongue, and mouth symptoms, but also a characteristic response to appropriate treatment.

We have recently had the opportunity to study in detail a

central pallor. Four megaloblasts were seen. The platelets were normal in numbers but many were larger than normal. The reticulocyte count was 0.4 per cent.

The blood calcium was 8.8 mg. per 100 and the direct and indirect Van den Berg reaction negative. The twenty-four-hour stool contained a marked excess of fat, 32 Gm.; fatty acids, 25.8 Gm., and neutral fat, 6.2 Gm. Fractional gastric analysis after the injection of 0.25 mg. of histamine again showed an essentially normal secretory function:

	Total acid.	*Free HCl.	Combined acid.
Before.....	32	16	12 cc. 1/10 N. NaOH
15 minutes after.....	60	36	20 " "
30 minutes after.....	44	22	14 " "
45 minutes after.....	60	38	20 " "
60 minutes after.....	44	30	14 " "
1 hour, 15 minutes.....	40	30	8 " "

Urinalysis was negative.

x-Ray examination of the gastro-intestinal tract showed no evidence of a lesion involving the stomach or duodenum. The coils of jejunum were dilated suggesting a lack of tone. There was a reduplicating loop of the descending colon, no indication of obstruction or malignancy. The observation on the forward progress of the meal through the small intestine pointed to a disturbance of motor function, and a delay up to four hours in the passage of the meal into the colon, without evidence of mechanical obstruction.

The intracutaneous tuberculin test was quite strongly positive but no other indication of tuberculous disease was demonstrable.

The normal values obtained on fractional gastric analysis, the negative indirect van den Bergh reaction, the fatty diarrhea, the extreme emaciation, the low blood calcium values, the decrease in size of the liver, and the absence of subacute combined sclerosis constituted strong evidence against the diagnosis of pernicious anemia despite the blood picture which fulfilled all requirements. These same factors together with the presence of normally split fat in the feces, with the diarrhea at times white or gray and frothy and matutinal in character, with the marked and constant abdominal distention, and the history of sore mouth and tongue, pointed more directly to the diagnosis of nontropical sprue even in the absence of very definite gastric symptoms.

She was placed at once on the low fat, low carbohydrate, high protein diet advocated by Fairley,⁸ Lilly liver extract No. 343 equivalent to 600 Gm. of whole liver, 30 grains calcium lactate, 30 drops viosterol, 15 grains pancreatin and 1 drachm vitavose daily. There was marked and immediate improvement. The stools became less numerous, the distention much less and the appetite increased to such a degree that it seemed advisable to increase the diet to 1800 calories after four days. This initial gain was not maintained, however, and the distention, diarrhea, and anorexia recurred. Although the initial dosage of liver resulted in improvement of the red cell count, a slight reticulocyte response, and a fall of the color index below unity, the lack of gain in other directions suggested inadequate assimilation. For

In October of 1927 moderately severe anemia with low color index had recurred and the stained smear showed slight anisocytosis. Nine months later the color index had risen to 1.1 associated with the appearance of many macrocytes, poikilocytes, and anisocytosis. In the subsequent examinations the constant presence of achromia, poikilocytosis, and anisocytosis is noted. Occasional normoblasts have been present since August, 1931, but megablasts were not seen. For the most part the leukocyte count was within normal limits although on two occasions it was just over 4000 per cm. with a slight reduction in the number of polymorphonuclear cells and corresponding increase in lymphocytes.

In November, 1929, when the color index was 0.4 with an approximately normal erythrocyte count, the urine contained no urobilin. Stool examination at this time showed a soft semiformed fawn-colored fecal mass with metallic luster and a sour odor. Blood and mucus were absent but meat fibers were present in excess, many poorly digested. Free fat was present in moderate amounts and there was a marked excess of fatty acid crystals with occasional soap crystals. Fractional gastric analysis revealed a normal secretory function:

	Free HCl.	Total acid.	
15 minutes.....	30 cc.	46 cc.	1/10 N. NaOH
30 minutes.....	50 "	70 "	"
45 minutes.....	42 "	62 "	"

She was admitted to the Medical Service of the Fifth Avenue Hospital on August 18, 1932. Physical examination revealed marked emaciation and extensive pigmentation from the sun of exposed skin areas. While the integument was dry and lacked the normal turgor, neither the dermatitis nor the symmetrically disposed atrophy of pellagra were present. The pupils and the fundi were normal. Many teeth were missing and several of those remaining were in bad condition. Moderate pallor of the mucous membranes was present. The tongue was fissured and showed atrophy of the papillae along the lateral margins and the tip, but no aphthae or acute inflammation. The lungs were clear and apart from a blowing apical systolic murmur the heart was normal. The abdomen was greatly distended, tympanitic throughout, and dilated coils of intestine with slow waves of peristalsis were clearly outlined through the greatly thinned parietes. The liver and spleen could not be felt but on percussion the former seemed much reduced in size. Slight edema was present over both feet and lower legs. Detailed neurological examination revealed no evidence of impairment of the central or peripheral nervous system. The Chvostek sign was slightly but definitely positive.

The laboratory examinations on admission to the hospital were as follows: Hemoglobin, 70 per cent; red blood cells, 3,300,000; color index, 1.06; leukocyte count, 5100; polymorphonuclears, 62 per cent; lymphocytes, 35 per cent; monocytes, 3 per cent. In the stained smear there was very marked anisocytosis and poikilocytosis, with the erythrocytes ranging from 4.5 to 13 μ . Many micropoikilocytes, macropoikilocytes, microcytes and macrocytes were present but the picture as a whole was definitely megalocytic. Numerous cells showed polychromatophilia, and many were achromic with marked

been increased too soon and on August 30th it was reduced to 1300 calories in the attempt to induce as complete gastro-intestinal rest as possible although additional weight loss was inevitable.

During the ensuing period up to September 19th her general condition became progressively worse. Further emaciation occurred, the diarrhea and distention persisted unchanged, edema of the lower extremities increased and extreme mental depression set in. The situation became exceedingly grave and it was obvious that some drastic alteration of treatment was imperative. Accordingly on the 19th the diet was again raised to 1800 calories, the dosage of liver extract by mouth was maintained, and the parenteral preparation in amounts equivalent to 100 Gm. of whole liver given intravenously each day in place of the intramuscular route. Apart from slight flushing of the skin and sense of throbbing in the head these produced no unpleasant symptoms when given slowly. Within twenty-four hours of the first intravenous injection a most extraordinary subjective and objective improvement occurred. Marked change in morale and increase in appetite were immediate, and the edema which was associated with lowered serum albumin and globulin values, completely disappeared in four days. The diarrhea, however, continued and despite negative results of further search for the *Amoeba histolytica* or *Bacillus dysenteriae*, an additional course of anayodin was given with little or no effect.

On the morning of September 26th an acute generalized attack of tetany occurred, the Trousseau and Chvostek signs were marked, and definite trismus and stiffness of the hands and fingers were present for several hours, recurring in milder form from time to time during the next five days. Blood taken immediately showed a calcium value of 4.9 mg. per 100; 30 cc. of 10 per cent solution of calcium gluconate were given intravenously and 10 units of parathyroid extract subcutaneously. This treatment was continued for the next eight days with 10 cc. of the solution intravenously, 15 grains by mouth, and 20 units of parathyroid extract subcutaneously. On the 28th the blood calcium had risen to 5.9 mg. per 100 with phosphorus 5.1 mg. per 100, and on October 4th the values were 8.9 and 4.6 mg. per 100 respectively. No recurrence of tetany developed and the Chvostek and Trousseau signs gradually disappeared.

Intravenous and oral administration of liver was continued without change until October 6th. The stools became formed averaging one to two a day, appetite remained excellent, and the distention was much less. She failed, however, to maintain the initial improvement in blood values. The color index remained 0.9 but the erythrocyte count had fallen on the 4th to 2,900,000 and the hemoglobin to 54 per cent. The liver extract, therefore, was stopped and 3 Gm. of reduced iron a day substituted. This was followed by a dramatic blood response. On the seventh day the reticulocyte count reached 3.8 per cent, and on the eleventh day the red cell count was 4,800,000 and the hemoglobin 71 per cent, while the average cell diameter had fallen to normal. In other respects the picture was much less favorable. Diarrhea and distention recurred associated with loss of weight. The appetite fell off and the tongue became red and tender.

Resumption of liver extract intravenously each day in amounts equivalent

this reason the equivalent of 100 Gm. of liver in the form of the parenteral preparation given intramuscularly was added on September 1st, and a similar



Fig. 43.—Gastro-intestinal x-ray examination showing dilated coils of jejunum.

increment on the 12th, but without significant effect. The persistence of from two to five liquid stools a day, and the distention suggested that the diet had

both in the cell count and in hemoglobin. Midway during this period the resumption of daily intravenous injections of liver extract were associated with symptoms suggesting an allergic state and intracutaneous injection produced a marked wheal and erythema but similar tests on two control individuals who had not had liver extract were also markedly positive. Coincidentally a critical fall in the blood values occurred, which ceased with

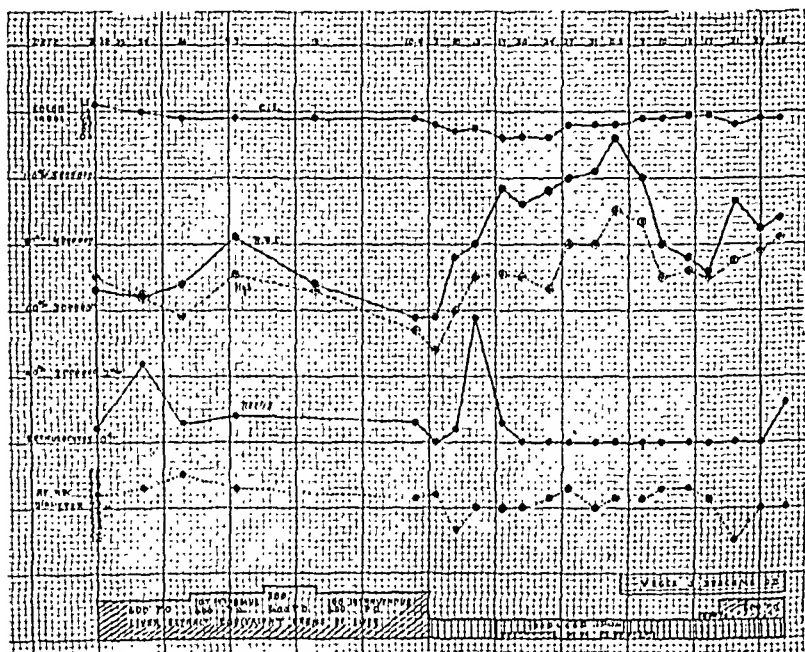


Fig. 44.—Variations of the hematological condition under different types of therapy from August 18th to November 28th.

withdrawal of this form of therapy. It is impossible to explain the mechanism but it appears that the extract when used intravenously may, under certain conditions, induce a rapid fall in blood values.

During the final period of observation, iron and liver extract by mouth restored the blood values to normal, the color index remained below unity and the average cell diameter re-

lent to 100 Gm. of liver in addition to the iron by mouth promptly checked these symptoms and restored a normal sense of well-being. The attempt was then made further to reduce liver therapy. In the course of the next nine days three injections of similar amounts were given. On November 3d, at the end of this period, it was obvious again that progress was unsatisfactory. Further loss of weight had occurred, the stools again were too numerous and of poor consistency, and distention and dyspepsia were troublesome. The tongue was definitely red and tender. The Lederle parenteral extract was substituted and given intravenously each day in comparable amount until the ninth when it was discontinued. During this period the mouth condition, appetite, diarrhea, and morale all improved decidedly but the patient complained of some paresthesia of the hands and face during the injection and within the week the red cells fell from 5,600,000 to 4,000,000 and the hemoglobin from 90 per cent to 70 per cent.

On November 4th, 1 drachm vegex three times a day was substituted for vitavose, and following the complete withdrawal of liver the general condition continued to be satisfactory. Stools again improved, appetite and morale became decidedly better, and the distention less constant. On November 16th the Lederle oral preparation of liver extract was begun and increased three days later to the equivalent of 600 Gm. of liver, although the troublesome symptoms previously noted had not recurred.

Comment.—Judged by the criteria set up by Manson-Bahr this case is atypical in two respects. Control of the diarrhea and distention has been difficult and not entirely satisfactory, and gain in weight has not occurred. Poikilocytosis and polychromatophilia have been more marked than is usual in sprue. The history and the clinical picture as a whole have been quite characteristic however. Apart from the occurrence of severe acute tetany with recovery, the variation in the response of the blood values to different forms of treatment constitute the feature of special interest (Fig. 44).

Castle and Rhoads noted that in certain instances the anemia of sprue failed to respond satisfactorily without the exhibition of iron, and this is clearly shown in this case. During the initial period of six weeks liver without iron was used. This produced and maintained a shift of the color index to less than unity, a primary rise in the red cell count and hemoglobin, followed by a sustained fall to levels below those on admission. The picture had changed from a hyperchromic to a hypochromic anemia. Withdrawal of liver and substitution of iron was followed by a typical secondary reticulocyte response and marked improvement

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turned to normal. Anisocytosis and poikilocytosis became somewhat less marked and nucleated forms disappeared.

The data obtained in this case indicate that the color index may be an important guide in the treatment of the anemia of sprue.

TABLE 1

Origin.	Number of cases.	Date.	Author.	
Georgia.....	4	1905	Graham quoted by Wood.	Atypical. No clinical details.
Georgia.....	?	1907	Harris quoted by Wood.	
N. Carolina.....	1	1914	Heath and Allen. ⁴⁰	
S. Carolina.....	1	1919	Wood. ³⁸	
South U. S. A.....	2	1920	Boyd. ⁴¹	
Louisiana & Mississippi	3	1921	Simon. ⁴²	
Texas.....	2	1921	Hannibal and Boyd. ⁶¹	
Massachusetts.....	1	1923	Blumgart. ⁴³	
Germany.....	1	1923	Schaefer. ⁴⁴	
Denmark.....	4	1925	Thaysen. ⁴⁵	
Holland.....	1		Van der Scher quoted Thaysen.	
Holland.....	1		Talma quoted Thaysen.	
Louisiana.....	1	1926	Musser. ⁴⁶	
Mid West U. S. A.....	1	1926	Lambright. ⁴⁷	
Denmark.....	1	1927	Holst. ⁴⁸	
Louisiana.....	3	1927	Silverman. ⁴⁹	Atypical. Atypical followed by pellagra. 1 atypical, no other descriptions.
Tennessee.....	1	1929	Fontaine. ⁵⁰	
Illinois.....	3	1929	Holmes and Starr. ⁵¹	
England.....	1	1929	Manson Bahr. ⁵²	
U. S. A.....	1	1929	Bloomfield and Wyc-koff. ⁵³	
Denmark.....	1	1929	Thaysen and Norgaard. ⁵⁴	
Virginia.....	2	1930	Porter and Rucker. ⁵⁴	
New York.....	1	1930	Mendelson and Beam. ⁵⁵	
S. Carolina.....	1	1930	Hines. ⁵⁶	
Alabama.....	30	1931	Marsh. ⁵⁷	
Virginia.....	1	1931	Campbell. ⁵⁸	Duodenal stenosis.
Illinois.....	1	1931	Marble and Bauer. ⁵⁹	
N. Central U. S. A.....	1	1932	Radl and Fallon. ⁶⁰	
Total.....	71 cases			

Five cases atypical, 36 cases without clinical description, 1 case with stenosis of duodenum equals 42 questionable cases.

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The nature and degree of mental involvement vary greatly, and range from mild personality changes and general nervousness and irritability to definite psychotic trends of the paranoid type. Stupor, apathy, and somnolence may be the symptoms first encountered. Tactile, visual and auditory hallucinations have been described. Delusions of reference, persecution, and expansion may occur. Mental symptoms resembling those of paresis or leading to a diagnosis of manic-depressive psychosis, or Korsakow psychosis are mentioned. In fact, it becomes apparent that there is no characteristic mental picture, but that most commonly, the symptoms are those which come under the designation of toxic psychosis.

The onset of the mental symptoms with reference to the anemia also varies. They may develop at any time during the course of the disease, even after the institution of liver therapy (Hackfield⁵). In some instances, however, as in the case to be described, they occur long before the anemia begins or is recognized.

Case Report.—O. T., male, aged forty-five years, was admitted to the Fifth Avenue Hospital, August 4, 1928.

Family History.—There is a definite history of nervous disorders on the father's side for two generations. His father, who had lived with him for fifteen years and died nine months before the patient's admission to the hospital, was queer, and possessed many odd traits. He would frequently wake up in the middle of the night and cry out, "I am dying." He would go to bed with his shoes on, for fear he would be compelled to get up quickly. He would never retire until his son came home. The father's sister was constantly fearful that something might happen to her and was always complaining. His paternal grandmother had paranoid ideas about the members of the family, and finally left the family. Patient's mother was an odd person also, and wrote books on occult subjects. The parents had been separated for forty years.

Chief Complaint.—Weakness, inability to walk or stand without complete exhaustion; afraid to be alone; cries and yells when alone; afraid of being in a crowd.

Personal History.—He could recall no serious ailments except diphtheria during childhood. He is a bachelor, and has never cared for the company of women. He has had no obvious homosexual contacts, but expresses a certain paternal attitude toward young men in whom he is interested and whom he likes to assist in business. He has been an accountant for eighteen years. He was rather slim until the age of twenty-eight, when he began to acquire weight. His best weight, one year ago, was 220 pounds, but he has lost about 30 pounds

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THE MENTAL SYMPTOMS OF PERNICIOUS ANEMIA AND THEIR RESPONSE TO LIVER THERAPY

It is generally taught that pernicious anemia is a disease which involves three important systems:

1. The blood and hemopoietic organs.
2. The gastro-intestinal tract.
3. The central nervous system.

It is not generally recognized, however, that mental symptoms are encountered more or less frequently, and that these symptoms are, at times, of paramount importance in the management of the case.

"The mind occasionally wanders," said Addison¹ in his classic description of the disease. Since then, a careful study of the literature reveals many accounts of various types of mental disturbances associated with pernicious anemia. The incidence of mental symptoms in pernicious anemia is given as 40 per cent by Weisenburg.² According to Woltman,³ in an analysis of 1498 patients seen in the Mayo Clinic, 4 per cent showed an outspoken psychosis, and 35.2 per cent presented lesser mental changes. Cabot,⁴ in a study of 647 cases, found mental symptoms in 15 per cent (102). He classified the cases into the following groups: delirium, 44; delusions, 14; hallucinations, 8; morbid psychosis, 13; dementia, 9; melancholia, 3; mania, 3; hysteria, 1. The above-mentioned statistics indicate that mental symptoms are not rare, and may constitute a serious complication in the treatment of the disease.

Course.—The patient was put on a high visceral diet with 200 Gm. of liver daily. He also received 20 minims of dilute hydrochloric acid three times a day. Within ten days there was a pronounced improvement in the blood picture, and he gradually recovered strength. It became easier for him to be alone in the room, and his general outlook on life became brighter. When he left the hospital, September 12, 1928, the hemoglobin was 110 per cent, and the erythrocytes numbered 5,200,000. At that time there was a complete resolution of the mental symptoms. His fears and anxieties disappeared, and he was able to start life again without the usual worries. After a short time, he was able to walk easily and without experiencing the fatigue which disabled him prior to his admission to the hospital. Six months later, he secured a remunerative position as an accountant which he has kept uninterruptedly during the next three years. Two years, after his discharge, he was married, and discovered partial impotence. He has been under observation for a period of three and one-half years, during which time he has been in good health. He has been eating liver at least three or four times weekly excepting for short intervals, throughout this period. A summary of the blood findings is given in the following table:

Date.	Hemoglobin.	Red blood cells.
8/ 8/28.....	30	1,500,000
8/13/28.....	43	1,900,000
8/16/28.....	45	2,200,000
8/20/28.....	66	3,300,000
8/23/28.....	70	3,500,000
8/31/28.....	94	4,500,000
9/ 9/28.....	94	4,950,000
2/11/29.....	110	5,200,000
8/30/29.....	107	5,500,000
4/18/30.....	109	5,400,000
5/ 6/31.....	114	5,700,000
2/15/32.....	104	5,500,000

Case Summary and Comment.—A case of pernicious anemia with slight central nervous system lesions, and a pronounced psychoneurosis. There is a definite familial neurotic background, and the patient's symptoms commenced about twenty years prior to the discovery of pernicious anemia. After the administration of liver for a short time, there was a rapid improvement in the blood picture, and the mental symptoms disappeared. They have not recurred during a period of observation of three and a half years.

Discussion.—In discussing the significance of the mental symptoms of pernicious anemia, two major problems immediately present themselves; namely, (1) the causal relationship

during the last year. He has been a heavy drinker of whisky for many years, and smokes 30 cigarets daily. He denies venereal diseases.

The mental symptoms have an indefinite beginning, but date back about twenty years, and have gradually increased in severity. He worries a great deal, and sleeps poorly. He is afraid to be alone, but a crowd, likewise, makes him fearful and shaky, and he becomes very anxious and perspires freely. On many occasions, he has hired a man to accompany him on his trips through the city. He has been financially improvident and spends his earnings rapidly, so that he is always in financial difficulties. During the last fifteen years, he has had short intervals during which the symptoms were not so marked, but he has never been entirely free. In December, 1927, he visited a neurological hospital, where a careful examination was performed, but which apparently did not include a blood count. A diagnosis of psychoneurosis was made, and the anemia was either not recognized or was not present at that time. A course of psycho-analytic therapy was prescribed, but on account of the expense involved this was never carried out.

In June, 1928, he began to lose weight rapidly, and became progressively weak. At the present time, he states, it takes him several hours to dress. He experiences great difficulty in walking or standing, not because of pain, but as a result of marked weakness. Occasionally, there are tingling sensations in the finger tips.

Physical Examination.—An obese male, weighing 193 pounds; height, 71 inches. He exhibited a marked lemon-yellowish color of the skin, and the mucous membranes were pale. The tongue was smooth and shiny, especially at the edges and anteriorly, and there was definite atrophy of the papillae. A hemic murmur was audible over the entire precordium. Heart was not enlarged and showed no abnormalities. Blood pressure, systolic 110; diastolic 60. The thyroid gland was not felt and no adenopathy was present. There was slight edema of both legs.

Neurological Status.—The positive findings were as follows: Moderate tremor of both hands; deep reflexes all diminished, especially the knee jerks; absent Achilles reflexes; pupils react sluggishly to light and during accommodation.

Mental Status.—There was no disorientation. The patient showed good insight into his condition, and was cooperative in answering questions and in his treatment. He was afraid to be alone in the room, and preferred to have an attendant present. He had frequent crying spells. He freely discussed his fears and difficulties as previously outlined.

Laboratory Data.—Blood count: Erythrocytes, 1,500,000; hemoglobin, 30 per cent; leukocytes, 5000; polynuclears, 70 per cent; lymphocytes, 28 per cent; monocytes, 1 per cent; eosinophils, 1 per cent. The smear showed marked poikilocytosis and anisocytosis, and polychromia. The reticulated cells numbered 5 per cent. The urine showed a faint trace of albumin, and an occasional granular cast. Blood Wassermann was negative. Icteric index was 8. Urea nitrogen, 8; and blood sugar, 83 mg. per 100 cc. Gastric analysis revealed no free hydrochloric acid, in the fasting specimen, and after an Ewald test breakfast the findings for free hydrochloric acid were: One-half hour, 0; one hour, 6; one and one-half hours, 14; two hours,¹ 16.

On the other hand, Lurie¹⁰ discovers a fairly uniform and definite relationship between the clinical and pathologic findings. He believes that in addition to the toxic action of the etiologic factor, metabolic changes also occur in the nerve cells as a direct result of the long-standing anemia. Likewise, McAlpin¹¹ infers that the mental symptoms and the neurological manifestations indicate the general effect of the neurotoxin on the central nervous system.

The literature discussing the effects of liver therapy on the mental symptoms is rather scant and contradictory. Smith¹² reports a marked improvement in the mental status of a patient with pernicious anemia after liver therapy. Warburg and Jorgensen⁷ also describe beneficial effects as a result of liver therapy in 6 patients. Similar reports are those of Bubert,¹³ and Emile-Weil and Cahen.¹⁴ Baker, Bordley, and Longcope¹⁵ review a series of 44 cases of pernicious anemia with central nervous system involvement. Of these, 7 showed psychic disturbances. After liver therapy, 4 were well and 2 improved. One was not followed.

Hackfield,⁵ on the contrary, in a study of 6 cases fails to discover any parallelism between the improvement in the blood picture after a liver diet and the psychotic symptoms. Whatever favorable change occurs in the mental status may be attributed to the general improvement in the health and vitality of the patient. In a very stimulating paper, he arrives at the conclusion that pernicious anemia acts only as an adjuvant in the precipitation or the aggravation of the psychosis, and therefore contends that a direct etiologic relationship between the pernicious anemia and the psychosis does not exist.

Finally, it must be added that in a large percentage of the cases reported in the literature, there is a hereditary predisposition to psychosis or some familial mental imbalance. Likewise, the history frequently reveals a personal neurotic background or a serious emotional conflict preceding the onset of the psychic symptoms. In this respect, moreover, it is necessary to bear in mind that a diagnosis of pernicious anemia with its fatal implication may be sufficient psychic trauma to elicit the

between the somatic lesions and the psychopathic disturbances; and (2) the effects of liver therapy on the mental status. With reference to the former, the literature, although quite extensive, is not convincing, chiefly because the majority of the cases recorded, date back to the era prior to the introduction of the Murphy-Minot diet in the treatment of pernicious anemia. In those days, pernicious anemia was a fatal disease, and there was no opportunity to follow the mental symptoms to their logical conclusion because the patient died from the effects of the anemia.

Langdon⁶ first expounded the theory that there was a group of patients in which nervous and mental manifestations preceded the development of pernicious anemia—a prepernicious anemia stage. This view is supported by Warburg and Jorgensen,⁷ who point out that there are cases in which psychosis and neurasthenia, megalocytosis, and achylia gastrica with glossitis are associated and in which the anemia is a late development. They assume a definite etiologic relationship between the anemia and the mental symptoms.

Barret,⁸ in a study of the cortex in 9 cases of advanced mental disease in which pernicious anemia was present, demonstrated distinct pathologic findings in eight. These included fatty degeneration with disintegration of the chromophilic substance of the cells, a diffuse increase of the neuroglia and swelling of the intimal cells of the blood vessels. He found focal lesions which corresponded very closely to the lesions characteristically present in the cord. Barret's conclusion is that the changes are not of a specific type, but rather those which occur in chronic intoxications.

Woltman,³ after reviewing the pathologic findings in the brains of pernicious anemia patients, comments that it is not possible to state definitely what influence these changes have in the production of the psychosis. They may contribute to its development, but they are found in patients without mental disturbances. He also believes,⁹ however, that the mild mental manifestations such as apathy and somnolence may depend on the brain lesions.

neurotic or psychoneurotic manifestations in a patient debilitated by a profound anemia and its associated disturbances.

Summary and Conclusions.—1. A case is reported of pernicious anemia with psychoneurotic symptoms which preceded the onset of the anemia by many years. After the administration of liver therapy, there was a rapid and lasting recession of the mental symptoms.

2. The causal relationship between the somatic lesions and psychic symptoms is discussed and the literature reviewed.

3. It becomes apparent that familial and personal predisposition are important factors in eliciting the psychotic symptoms.

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horse serum, and those harboring intestinal parasites such as *ascaris lumbricoides*. Nevertheless, Coca felt that, in order to differentiate the individuals sensitized by inoculation of sera from those who are spontaneously sensitive by virtue of heredity, the latter should be designated as atopic. An atopic individual therefore represents one who is naturally and spontaneously sensitive to foreign proteins; one who reacts with symptoms of hay fever, asthma, etc., on primary contact with the offending protein; has a family history of hypersensitiveness, and specific "reagins" in his blood.

Inasmuch as nonatopic individuals may on contact with certain foreign substances, like drugs or bacterial proteins, acquire and manifest reactions similar to those of atopic individuals, both types have been grouped together and designated under the term "allergic."

The term "allergy" for the present, therefore, may in contrast to atopy serve as a generic term to indicate both atopic and acquired sensitiveness to foreign proteins, chemical substances, and bacteria.

The ability to acquire sensitiveness in one form or another is probably universal. The reactions to specific antigens are evidenced by changes in the humoral, the different cellular tissues as well as neural structures, particularly the vegetative nervous system and its ramifications. The affected tissues which vary in each individual respond characteristically in the first place by alteration of their inherent function, and secondly, by organic change of an inflammatory and degenerative nature.

Inasmuch as similar reactions, regarded as the prototypes of human sensitization are to be found in the anaphylactic response of the sensitized animal following the injection of foreign protein living or nonliving, let us examine the character of the latter.

It is a well-known fact that the reacting tissues involved in the anaphylactic shock vary according to the animal species involved. In the sense of Doerr, such tissues constitute the dominating shock tissue. Thus death in anaphylaxis in the guinea-pig is centered in the lung, the bronchi are in a state of tetanic spasm, and the lung is enormously distended, etc. It

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ALLERGIC MANIFESTATIONS OF THE COMMON COLD

THE constitutional element in disease is an accepted fact. With the progress of the science of medicine, it acquires new connotations. One of these is the concept of allergy. Allergy, according to von Pirquet, means altered capacity on the part of actively sensitized animals to react to the original antigens. An example of this is to be seen when a guinea-pig is injected with an antigen like the tubercle bacillus. Within ten days following the inoculation the tissues of the tuberculous animal become so altered, *i. e.*, allergic that injection of a 1 : 10 dilution of O. T. is followed by marked skin reaction.

The term "allergy" was later used by the same author to describe reactions of man to foreign substances. Cooke, Van der Veer and Spain, however, by careful clinical studies have been able to demonstrate that certain individuals in the so-called "allergic group" are radically different from normal persons by heredity and possess the faculty of spontaneously reacting to foreign proteins. In other words, they are naturally hypersensitive. Prausnitz and Kustner, also De Besche, found that when the serum of such patients is injected intradermally into the skin of normal, nonsensitive individuals, it could so alter, or sensitize the area into which it was inoculated that skin reactions similar to those obtained in the allergic patient could be elicited on the artificially prepared site, by means of the incriminating test proteins. The specific factor in the serum of the hypersensitive patient capable of sensitizing the normal human skin has been called "reagin." Reagins, however, have also been found in normal patients who had been injected with

sensitiveness. These workers believe that this explained how different strains of streptococci may all induce a similar clinical and microscopical picture.

Zinsser and Grinnell, employing pneumococcus autolysates, were able first to sensitize guinea-pigs and later on injecting their joints with this material cause the development of swollen joints; whereas nonsensitized animals, in the absence of allergy, showed no such involvement.

Francis and Tillet, studying the allergic reactions in pneumonia patients following the crisis, were able to demonstrate in certain instances, definite urticaria-like skin reactions subsiding within two hours, with the specific carbohydrates fraction obtained from the particular pneumococcus causing the infection in the patient.

Consideration of the experimental data at hand, in spite of many gaps in our knowledge, led Zinsser to formulate the theory that in bacterial allergy "we are dealing with sensitization of the body by autolytically liberated antigenic substances, which are absorbed from any focus in which bacteria reacted to inflammatory tissues, and as a result of which the body is rendered subsequently sensitive to contact with the same autolytic products, whether they are liberated and absorbed from a chronically existent focus, or from an identical infection subsequently acquired."

In connection with the common cold, we are probably dealing not only with a filtrable virus which prepares the way so to speak for the pneumococci, streptococci, and staphylococci, etc., usually present in the upper respiratory passages, but we are confronted also with the fact that the pathogenicity of these secondary bacteria becomes increased. They may become resident within the mucous membranes of the upper and lower respiratory tract, and in predisposed individuals, following the subsidence of the acute phases of the cold may become responsible for the recurrent, subacute or chronic sinusitis, as well as unresolved pneumonia. In other words, these bacteria establish foci in various areas from which their products may be absorbed and sensitize like any other proteins the allergic individual, thus

is this state that caused Meltzer to suggest its similarity to bronchial asthma in man. In the rabbit, anaphylaxis is characterized by spasm and obstruction of the pulmonary vessels and circulatory collapse, while in the dog, the liver is the primary shock tissue. Compare this with human reactions to sensitization with foreign proteins and we note a striking parallelism.

Thus injection of horse serum into susceptible individuals or ingestion of egg white may induce in one asthma with or without death depending on the degree of sensitiveness; in another urticaria and arthritis, or gastro-intestinal symptoms simulating appendicitis, etc., while in some, circulatory collapse. In other words, the reactions will occur in that organ or tissue which represents the natural dominant shock organ in the patient affected.

Evidence of hypersensitiveness to soluble proteins such as egg or fish may be readily demonstrated in the allergic human being by means of skin tests. In dealing with bacteria and their products, however, this becomes somewhat more difficult in view of their complex nature.

Studies for the purposes of investigation of bacterial hypersensitiveness have been carried out by Avery, Heidelberger, Francis and Tillet, Zinsser, Landsteiner, Wells, and others. They found that the whole bacteria as well as their products, namely the nucleo-protein and carbohydrate fractions, under certain conditions are capable of producing allergic as well as anaphylactic reactions in every way similar to those brought about by the action of soluble protein substances nonbacterial in nature.

Sensitization to bacterial products of the hemolytic streptococcus group of bacteria, has been demonstrated by Zinsser and Grinell in 1925 and 1927 following the establishment of a chronic focus with these organisms, Dochez and Stevens, Mackie and McLachlin and Kirchner have made similar observations in scarlet fever and erysipelas. In connection with their studies in rheumatic fever, the manifestations of which they feel, are, in all probability, allergic in character, Derick, Hitchcock, and Swift were also able to demonstrate that a focus of infection with nonhemolytic streptococci may be followed by a state of hyper-

In these patients, there was no atopic component and no hyperirritability of the vegetative nervous system.

In a second category of cases under consideration were 409 cases of bronchial asthma. Here, as is well known, there is present a marked hypersensitivity of the autonomic nervous system which is partly responsible for the bronchospastic phenomena. In 19 per cent of these, asthma was due to protein hypersensitiveness as well as to infection of the sinuses and lungs following winter colds; in 28 per cent it was solely due to infection in the respiratory tract. In these groups, 9 cases were found which in the course of their asthma developed attacks of polyarthritis.

The usual history in these cases was that they never quite recovered from the cold which they contracted during the winter and out of a clear sky were seized with an attack of coughing followed by an asthmatic paroxysm.

Out of 132 cases of asthma with negative skin tests which were followed from three to four years, 87 were found to have sinus disease, the antra and ethmoids being chiefly implicated, while the rest had in addition pulmonary infections. In the sinus cases the lungs showed secondary bronchitis with no distinctive roentgen findings. The youngest patient in this group was eighteen, the oldest sixty-one. The average age of onset was 34.4 years. Evacuation of pus from the infected antra and local treatment of the ethmoids definitely controlled the attacks.

In the sinus-pulmonary cases, 22 had unresolved pneumonia, 4 were complicated by bronchiectasis, and 21 had sinus disease associated with unresolved pneumonia. The average age of onset was 38.4 years, the average duration of symptoms eight years. The youngest patient in this series was fifteen years of age, the oldest fifty-six. The shortest duration of symptoms was two years, the longest forty.

Attention was called to the importance of unresolved pneumonia as a responsible factor for asthma in a paper published in 1922. In following up these cases, it was noted that when they become free from attacks, especially during the summer months, the pneumonic infiltration disappears and the lungs apparently

rendering him more readily susceptible to exogenous or endogenous infection by the same or similar organisms.

In the last several years, we have been especially interested in the study of cases presenting allergic symptoms developed as a sequence of focal infections following a cold. These could be subdivided into three groups: (1) characterized by recurrent winter cough; (2) asthma, urticaria, and angioneurotic edema; and (3) asthma and arthritis. In every respect, these presented clinical syndromes comparable to the protein hypersensitiveness group.

The first series of patients consisted of 13 who with the onset of cold weather came to the clinic complaining of headache and dizziness, nervousness, and irritability, sweating at slightest exertion, general debility, pains in the chest and cough. The pains were either substernal or referred to the back on one side or another. On detailed inquiry, these patients stated that they had repeated colds or influenza, followed by persistent cough for a number of years, recurring every winter and diminishing appreciably during the summer. The duration of symptoms in the longest case was nine years, the shortest several weeks. Many of these patients returned yearly to the clinic with the same complaints, improving somewhat with symptomatic therapy. In the further study of the cases, it was found that they could be separated into three subdivisions. First, a group of seven in whom a tentative diagnosis of unresolved pneumonia was made in view of the history of recurrences of pulmonary infection for a number of years. The physical signs in the chest were borne out by x -ray findings. In view of the history of colds and headaches preceding the lung involvement, the sinuses were investigated as a possible focus for the infection in the lungs. These revealed involvement either of the antra, ethmoids, or both, confirmed by x -rays.

A second group of three, who on physical examination showed signs of bronchitis, negative x -rays of the chest, and positive of the sinuses, and a third group whose chests on physical examination showed pneumonic infiltration confirmed by x -rays but negative sinus x -rays. Of this group, 2 patients were found to have clinical sinus disease even though the x -rays were negative.

the joint manifestations. In the remaining four, there was a coexistent atopic hypersensitiveness to substances such as ragweed, goosefeathers, dog hair, rabbit hair, foods as well as dust. The elimination of these atopens alone influenced neither the asthmatic nor the arthritis attacks. It therefore seemed that infections in the sinuses and lungs were the exciting cause both of the asthma and of the arthritis. This was proved in 7 of the 9 cases by the fact that evacuation of pus from the infected antra and successful treatment of the diseased ethmoids, was followed by recession of the more recent pulmonary focus of infection and complete subsidence of the arthritis. The asthmatic attacks became milder, diminished in frequency, and the harassing cough ceased almost entirely.

During the warm weather all residual symptoms, referable to both conditions, disappeared as a result of the general beneficent effect of temperature and climate on chronic respiratory infections and their complications.

Additional unusual features noted in these patients were an episcleritis in Case I diagnosed by the ophthalmologist as evidence of a "rheumatic diathesis," meralgia paresthetica of the right leg in Case VI and right-sided sciatics in addition to the arthritis in Case VII.

Comparison of the duration of asthma and arthritic manifestation showed that whereas the asthma lasted on an average for ten years the average duration of arthritis was two years.

TABLE 1

Case.	Age.	Duration of asthma.	Duration of arthritis.
I.....	47	14 years	2 years
II.....	51	20 "	4 "
III.....	49	13 "	1 "
IV.....	54	18 "	1 "
V.....	36	8 "	3 months
VI.....	57	6 "	1 year
VII.....	36	18 "	2 years
VIII.....	59	50 "	2 "
IX.....	47	13 "	4 "

A number of years had intervened between the onset of asthma of the joint manifestations. The discrepancy in time relation-

ALLERGIC MANIFESTATIONS OF COMMON COLD

heal; the only residuums of the pathologic process being adhesions to the diaphragm. In our experience, patients presenting a picture of asthmatic bronchitis in whom roentgen examination reveals nothing but adhesions at the bases, should be suspected of having previously had inflammatory involvement of the lung parenchyma. They may still harbor a low-grade infection in the interstitium of the lung or their dilated bronchial walls, invisible with the roentgen ray, responsible for the cough, the thick tenacious mucopurulent expectoration. I feel that the persistence of the interstitial pulmonary inflammation, which serves as an important focus of infection, as seen in an exaggerated manner in the more fulminating cases at autopsy with associated bronchiectasis is usually found, unquestionably plays a rôle in the difficulties encountered in clearing up these conditions. The chronic bronchitis serves to obscure the deeper and more extensive lesions within the lung parenchyma.

To what extent latent sinus involvement is responsible in keeping up the pulmonary process may be evaluated in comparative observations in two series of cases. In an earlier group of 57 nonsensitive asthmatic patients observed between the years 1923 and 1927, only 7 showed a combined sinus and pulmonary infection; in a later series of 45 cases, 14 showed such combined infection. The latter was studied during 1928 and 1929, when greater experience led us to investigate the sinuses more thoroughly.

Asthma and Arthritis.—Nine patients developed arthritis in the course of their asthmatic attacks. Their ages varied from thirty-six to fifty-nine. Six were female and three male.

The character of the arthritis from which they suffered was migratory, affecting the wrists, fingers, shoulders, ankles. It was accompanied by moderate redness and swelling, pain on motion and often persisted for several weeks. The body temperature was not elevated. In 3 cases, x-ray examination revealed mild proliferative changes in one joint. In the remaining 6 no anatomical changes were noted in any of the affected joints.

In 5 of these patients, foci of infection in lungs and sinuses constituted the etiologic factors both for the asthma as well

the joint manifestations. In the remaining four, there was a coexistent atopic hypersensitiveness to substances such as ragweed, goosefeathers, dog hair, rabbit hair, foods as well as dust. The elimination of these atopens alone influenced neither the asthmatic nor the arthritis attacks. It therefore seemed that infections in the sinuses and lungs were the exciting cause both of the asthma and of the arthritis. This was proved in 7 of the 9 cases by the fact that evacuation of pus from the infected antra and successful treatment of the diseased ethmoids, was followed by recession of the more recent pulmonary focus of infection and complete subsidence of the arthritis. The asthmatic attacks became milder, diminished in frequency, and the harassing cough ceased almost entirely.

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The second source of evidence of bacterial allergy is indirect and based on the report of Cook who states that in about 20 per cent of cases he was able to induce asthmatic attacks at will with the subcutaneous injection of specific organisms in the form of vaccine, recovered from the mucosa of infected antra. These observations are important inasmuch as they parallel the findings in atopic patients in whom asthmatic attacks may be provoked by means of specific proteins.

It is obvious from this rather brief summary that allergy is a part of the immunological mechanism accompanying infection. While it may be possible to distinguish bacterial allergy from bacterial anaphylaxis, experimentally, in human disease both of these processes are undoubtedly concurrent.

Given a chronic focus of infection, the subsequent clinical phenomena will evolve in accordance with the constitutional make-up of the individual and the nature of the shock tissues affected, whether confined to special cellular, humoral or vegetative nervous system. Thus when the shock tissue is the lung, the effect of bacterial hypersensitiveness may take the form of a characteristic asthmatic attack. If it is the skin, it may appear as urticaria, eczema, or angioneurotic edema; in the joints, as arthritis.

Since the mechanism of bacterial and protein hypersensitiveness has been shown to be the same, similar clinical pictures may be expected to follow. The pathologic lesions in both may be characterized by sterile exudative and inflammatory phenomena. Such inflammatory reactions which may even go on to necrosis have as their analogue the Arthus phenomenon. This is a form of local hypersensitiveness which has been demonstrated by Opie, working with soluble proteins such as egg white, etc., to be dependent on the local interaction between antigen and precipitating antibodies.

In the dealing with bacteria, it is conceivable that the same phenomena may take place. According to Zinsser, these are due to autolytically liberated antigenic substances absorbed from a chronic bacterial focus which may render the body sensitive to subsequent contact with the same autolytic products, whether

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eliminate such a focus if possible. In my experience conservative measures are best. In the earliest stages, when it is confined to the sinuses, prompt evacuation of pus from infected antra, tamponage by means of silver preparations of diseased ethmoids, rest, etc., is followed by relief of symptoms. In the more chronic cases this type of treatment must be pursued for long periods of time. Here some allergists also advise vaccines, either autogenous or stock, as an additional form of therapy. In my experience the use of vaccines as a supportive measure is sometimes helpful, but their effect must usually be regarded in the nature of non-specific protein therapy. Typhoid vaccine subcutaneously in 0.5 cc. doses, twice a week at times, controls the harassing cough just as any other type of vaccines. Neither cures the disease.

Surgical interference of sinuses with the exception of the rare instances where the patient's focus is essentially in the antra is not satisfactory. Radical sinus operation may have to be resorted to but we must be sure that no atopic hypersensitiveness is present and sinus infection is the only etiologic factor in the allergic manifestations. Only then can we expect favorable results. If radical operation is decided upon, it should be done in two stages. The physician should be prepared for a possible postoperative reaction in the form of a "status asthmaticus," following such procedure. This should be treated with administration of oxygen and sedation, employing such drugs as sodium amytal, etc. Morphine should be used with circumspection, because of a possible morphine idiosyncrasy.

Tonsillectomy should be especially avoided in chronic infectious asthmatics. I have yet to see any relief of asthma arising therefrom. The impossibility of eradicating every focus within an infected respiratory tract, replete with adenoid tissue harboring incriminating bacteria is too obvious. The spreading of infection to other parts of the body by traumatizing tissue in course of operations is much more likely to affect an individual who is readily susceptible to these bacteria by virtue of his allergic state.

Change of climate to a warm, dry locality is much more effective in these cases. The experience of Coburn and his

liberated and absorbed from a chronically existent focus or from an identical infection subsequently acquired.

Inasmuch as these antigenic substances are necessarily complex, not only sensitizing nucleoproteins and toxins may be operative, but depending upon the invading organism, additional primary toxic effects will necessarily complicate the picture and influence the clinical course.

While it must be borne in mind that the presence of an infection within the lungs may induce bronchospasm and asthma by direct effect of bacterial action on the vagus branches within the bronchi in the constitutionally predisposed, it is a clinical fact that many asthmatics cease having attacks during an acute pneumonia when the infection is at its height or in the course of intercurrent infections such as typhoid, tonsillitis, etc.

It is in the presence of the more chronic focus, when the original acute infection has become quiescent that the patient presumably becomes sensitized to the bacterial products and the asthmatic attacks take place. The fact that infected antra are more often responsible for asthmatic attacks in contrast to the ethmoids where drainage is better, speaks for absorption of bacterial products rather than direct action of bacteria on the bronchial mucosa.

The assumption that the arthritis is dependent on the same mechanism as the asthma is necessarily based partly on circumstantial and partly on factual evidence. It is founded firstly on the analogous syndromes seen in essentially atopic states, *i. e.*, following the injection of soluble foreign proteins such as horse serum, etc.; asthma, arthritis, and urticaria may supervene. Secondly, on the facts that the infectious asthma on our cases admittedly due to bacterial allergy, and the arthritis, were due to the same bacterial focus.

The allergic nature of the arthritis is furthermore supported by the observations of Zinsser to the effect that "experimentally, in bacterial allergy, sensitiveness of joints can be demonstrated to be somewhat parallel to general sensitiveness."

Treatment.—In view of the importance of the chronic focus of infection as the sensitizing factor the logical treatment is to

allergy is generally accepted to be the responsible mechanism. Coexistent arthritis due to the same focus is in all probability an expression of similar reaction in allergic individuals, in whom the lungs are the primary and the joints the secondary shock tissues.

Direct proof of bacterial allergy by means of skin tests is difficult in the present state of our knowledge. Interpretation of the nature of the asthma-arthritis syndrome in our patients on the grounds of allergy to bacteria is based, therefore, on experimental and clinical observations.

associates with rheumatic fever patients in Porto Rico serves an important lesson in bacterial allergy. The practical disappearance of hemolytic streptococci from the throats of rheumatic patients followed by diminution in rheumatic attacks in contrast with a control group of rheumatic cases living in the north is striking. Purely infectious asthmatics, as is well known, are free of attacks during the summer, unless there is an associated atopic component such as sensitiveness to pollens, inhalants or food. When atopic hypersensitiveness is present no result can be expected unless that factor is properly disposed.

Removal to a warm, dry climate serves to bolster the resistance of the infectious asthmatics in that (a) the physical factor of "cold" is eliminated, (b) the incriminating bacterial flora may disappear.

Summary.—In summarizing these studies, we may say that recurrent winter cough and bronchial asthma due to chronic focal infections in the respiratory tract are allergic manifestations, occurring as a sequence to the common cold.

In a study of 409 adult asthmatics, 19 per cent were found to be due to protein allergy and focal infections in the sinuses or lungs, and 28 per cent to infection in the respiratory tract alone. Nine cases in this group were found to have both asthma and arthritis due to the same etiologic agents affecting the bronchial asthma, namely infection in the sinuses and lungs as well as atopic hypersensitiveness.

Simple elimination of atopens had no influence on either the asthma or arthritis as long as the focal infections were present. Both in the cases of recurrent winter cough and in the purely infectious asthmatics as well as in the 19 per cent of patients in whom atopy and infection were responsible agents, evacuation of pus from antra, treatment of the ethmoid and the subsequent recession of the pulmonary focus controlled the cough and asthmatic symptoms.

In 7 of 9 cases who suffered from asthma and arthritis, the arthritis completely subsided, while the asthmatic seizures diminished in frequency and severity as a result of therapy.

In asthma induced by a chronic focus of infection, bacterial

laden with micro-organisms, epithelial cells, and leukocytes. The submucosa is swollen and edematous and there is, in many cases, a peribronchitis with peribronchiolitis.

Physiologic Disorders.—For the production of a cough, there must be a reflex coughing arc. The cough center is probably in the floor of the fourth ventricle, close to the respiratory and vomiting centers. The peripheral sensory and motor nerves of the coughing arc are distributed along the respiratory system with special hypersensitive regions in the larynx, trachea, and large bronchi. The toxemia of whooping cough lowers the threshold of the cough center so that the slightest reflex irritation causes a shower of spasmodic contractions of the respiratory system. Many characteristics of whooping cough point to its being, besides an infectious disease, a neurological disorder. In favor of its being a neurosis are: the severity of pertussis in nervous children; the afebrile disorder; the paroxysmal nature of the disease; the apparent well being of the child between the paroxysms; the suddenness of the cough in response to slight physical or psychic stimuli, and the general nervous irritability. Whooping cough may be considered as a bacterial, infectious disease with a reflex neurosis probably of an allergic nature caused by the bacteria or their toxins affecting the peripheral or the central region of the coughing arc. The proximity of the cough center to the respiratory and the vomiting centers accounts for many of the respiratory difficulties and the frequent vomiting in pertussis.

Complications and Sequelae.—The venous engorgement during the paroxysms of coughing frequently gives rise to hemorrhages in various parts of the body. Bronchopneumonia is the most important respiratory complication. Bronchitis, emphysema, atelectasis, and tracheobronchial lymphadenitis are not uncommon. The heart is occasionally enlarged due to the severe strain of coughing and myocardial weakness. There is frequently a leukocytosis with a lymphocytosis. Vomiting is quite common, leading in many cases to malnutrition. Nephritis occurs in some cases and glycosuria has also been found. Injury to the brain by the toxemia, vascular congestion or hemorrhage is not a rare

CLINIC OF DR. J. EPSTEIN

GERMAN POLYCLINIC

PERTUSSIS AND ITS TREATMENT WITH GOLD TRIBROMIDE

PERTUSSIS is one of the most common communicable diseases of childhood affecting all races in all climates. It varies greatly in its epidemiology, virulence; intensity, and seasonal prevalence. The disease is probably caused by the bacillus pertussis which affects the upper respiratory system and leads to many pathologic and physiologic disorders. The infection is transmitted largely by direct contact; rarely by indirect. One attack usually confers a lasting immunity.

History.—Glimpses into the distant past and the middle ages seem to show that whooping cough was prevalent then but was not known as a definite disease entity. Ballonius in 1578 described an epidemic of pertussis in Paris. Thomas Willis in 1658 gave an account of an epidemic of pertussis in London. Thomas Sydenham was probably the first to study the disease in its various phases and described it in 1670. Whooping cough in an epidemic form appeared in Germany in 1724. During a widespread epidemic in Europe in 1732, the disease was carried to America. At present, whooping cough is prevalent in epidemic or endemic form throughout most of the world.

Pathologic Disorders.—The chief pathologic disorder in pertussis is a catarrhal inflammation of the upper respiratory tract with degeneration of the ciliated epithelium in which the bacillus pertussis is present in great numbers. This organism, also known as the Bordet-Gengou bacillus, belongs to the influenza group and is often found in symbiosis with the influenza bacillus. The mucous membrane secretes a thick, whitish, tenacious substance

Not uncommonly, after the disease has long subsided and the child is well for many weeks or even many months, there is a recurrence of the paroxysmal cough. This is usually not a recrudescence of whooping cough. It is probably due to some mild upper respiratory infection causing a reflex stimulation of the coughing center which remains for a long time in a hyper-irritable state as a result of the previous, prolonged, repeated attacks of coughing. After an attack of whooping cough the neuromuscular coughing system is in a state analogous to the physiologic condition which is known as summation of stimuli.

Treatment.—At the present time, a host of drugs are being used indiscriminately on the theory that, in this unyielding disease, one drug is as good as another. Vaccines have held and, to some extent, still hold the therapeutic stage with good, bad, and indifferent results. Their hypodermic use is a source of terror to children. Ether, given intramuscularly or by rectum, has been in vogue for some time but has proved of little value and much discomfort. x -Ray treatments over the chests of whooping cough patients have been tried but have not gained much therapeutic popularity. Carbon dioxide inhalations were suggested but they are not feasible in every-day practice.

In my study of whooping cough and its treatment, I divided all antiwhooping cough drugs in common use into hypnotics, sedatives, and antispasmodics and gave each group a careful and thorough trial in a fairly large number of cases. The results were not encouraging. I then made a special study of the bromides and classified them as univalents or monobromides, bivalents or dibromides and trivalents or tribromides. Potassium bromide (KBr), sodium bromide ($NaBr$), lithium bromide ($LiBr$), and ammonium bromide (NH_4Br) are univalent bromides. Calcium bromide ($CaBr_2$) and strontium bromide ($SrBr_2$) are bivalent bromides. Gold bromide ($AuBr_3$), iron bromide ($FeBr_3$ or Fe_2Br_6), arsenic bromide ($AsBr_3$), and aluminum bromide ($AlBr_3$) are trivalent bromides. In observing the action of the bromides, I found that the dibromides gave better bromine action than the monobromides and the tribromides were more effective than the monobromides or the dibromides. Of the tri-

complication, and leads to convulsions or other cerebral disorders. Chronic bronchopulmonary disorders and tuberculosis as a sequel to whooping cough are not uncommon.

Morbidity and Mortality.—Whooping cough may occur at any age but the greatest susceptibility is during the first half of the first decade of life. There are no definite statistical data on the morbidity of pertussis and the exact number of cases is not known. Since the disease is universal and there is only a slight natural immunity to it, the number of whooping cough cases must be very large.

The death rate from whooping cough per 100,000 population in the registration area in the United States for the last thirty years averages 9.92. Dividing the thirty years into three decades, there is evidence of a slight gradual decrease in mortality. In the first decade, the mortality rate per 100,000 population was 11.38; in the second, 10.46; and in the third, 7.94. The younger the child, the greater the mortality. Under one year of age, the mortality is about 20 per cent; between one and two years, 10 per cent; between two and three years, 5 per cent; between three and five years, 3 per cent, and between five and fifteen years, 2 per cent. After fifteen years of age, the disease is very rare. The number of children dead in the United States from pertussis is estimated to be over 10,000 a year. When the deaths due to the various complications and sequelae are added to this number, the total death rate is about 25,000 a year.

Diagnosis.—When the disease is fully developed, the diagnosis is very simple. During the first or catarrhal stage, and in mild or atypical cases, the diagnosis is sometimes difficult. A history of exposure to pertussis; a persistent spasmodic cough with a tendency to be worse at night; a negative finding on physical examination and an apparently well child between the paroxysms is diagnostic of whooping cough. In the majority of cases, there is no need for a bacteriological, serological or hematological diagnosis. The cough due to the onset of measles, spasmophilia, enlarged tonsils and adenoids, enlarged tracheo-bronchial glands or a foreign body in the respiratory tract may, for a time, simulate whooping cough.

tribromide is hygroscopic, unstable and difficult to dispense, I am using, in most cases, a uniform, standard preparation known as Elixir Gold Tribromide.

Gold Tribromide by Inhalation.—Since the soluble salts of gold are antibacterial even in a solution of 1 part to 5000, it occurred to me that it would be of therapeutic value if gold tribromide were given by steam inhalation in addition to its oral administration. After experimenting for a while, I found that when a teaspoonful of the aqueous solution of gold tribromide or the elixir is added to an ounce of water and the whole amount gradually converted into steam, it carried traces of metallic gold and gold tribromide. When this comes in contact with the raw and irritated mucous membrane of the respiratory tract, it has a soothing and antiseptic effect. The steam can be made in a croup kettle, teapot or any small vessel.

Result of Treatment.—The result of the treatment with gold tribromide in about 75 whooping cough cases from my own practice and from other observers was most gratifying. After two or three days of treatment, the cough was less frequent, the attacks were shorter and milder and the children slept better. In three or four weeks, the cough gradually ceased.

Summary.—As a result of a study of various drugs, especially the bromides, in the treatment of pertussis, I found gold tribromide to be an effective remedy in a large number of cases. The drug is soluble in water and is given by mouth, thereby avoiding the difficulties and the unpleasant after-effects of hypodermic injections or rectal medication. The Elixir Gold Tribromide is a stable, reliable preparation and is readily taken by children. Steam inhalation, charged with traces of gold tribromide, is very helpful. The earlier in the disease the treatment is begun, the quicker and better the results. Failure in therapeutic results may be due to errors in diagnosis, insufficient dosage, complications or to a specially virulent organism. The compound of gold tribromide inhibits the coughing reflex arc, allays the general nervous irritability and relieves the spasmodic attacks which cause violence to every system of the body.

bromides, the most suitable preparation for medicinal purposes is gold tribromide. This drug I have used in whooping cough with the most gratifying results.

Gold in Medicine.—Gold has been used for ages in the treatment of disease. The chief preparations of gold which have been employed are the metallic gold in a finely divided state, the oxide, the chloride, the bromide, the cyanide, and the thiosulphate. The soluble salts of gold are germicidal in strengths of from 1 part in 500 to 1 part in 8000 according to the species of bacteria. Various preparations of gold have been highly lauded in the treatment of tuberculosis and syphilis. In 1889, Goubert asserted before the French Academy that gold tribromide is more efficacious in petit mal and in many spasmodic conditions than are any of the other bromides.

Gold in Whooping Cough.—In my study of gold in whooping cough, I used the tribromide of gold. This is a neutral salt of gold and hydrobromic acid and has no free acid. It is brownish-black in color, soluble in water, deliquescent, and contains about 45 per cent of gold. The therapeutic effect of gold tribromide in pertussis is probably due to the sedative action of the bromine ion and the antibacterial effect of the gold ion. The compound of gold tribromide reduces the reflex irritability of the cough center and causes general sedative and antispasmodic action. It shortens the period of the illness, diminishes the number and severity of the paroxysms, gives the child rest and sleep and prevents complications. Gold tribromide may also be used with good therapeutic effect in bronchial asthma, chorea, migraine and petit mal.

Treatment of Whooping Cough.—Whooping cough children should be segregated when possible. When the cough is very severe and frequent, rest in bed in a semireclining position will be of decided benefit. Plenty of fresh air, sunshine, and good food is an essential part of the treatment. Gold tribromide should be given in an aqueous solution by mouth three or four times a day and once at midnight. The dosage varies with the age and condition of the child and the frequency of the coughing spasms. As a general rule, 1/10 to 1/20 grain should be given. As gold

vagus nerve,^{7, 8, 9} (b) sudden interference with impulse formation and propagation in the auriculoventricular node,^{10, 11, 12} (c) cessation of ventricular contraction in the presence of persistent auricular activity during complete heart block,¹³ and finally (d) to the various grades of acceleration of the ventricles with periods of reexcitation leading to transient ventricular fibrillation.¹⁴

THE VAGAL TYPES OF STOKES-ADAMS ATTACKS

For many years the French clinicians and in particular Charcot¹⁵ and Brissaud¹⁶ have taught that the alterations in the cardiac mechanism observed during Stokes-Adams seizures were of secondary importance. They believed that intrinsic changes within the bulbar centers and in particular arteriosclerosis of the cerebral vessels supplying these was responsible for the paroxysmal syncopal attacks. Bradycardia of the heart, in their opinion, appeared as a result and was not the cause of the cerebral anemia.

The fallacy of these assumptions is well appreciated today since it has been possible to correlate the successive neurological events ending in unconsciousness that follow the changes in the heart rhythm.

As a matter of fact, while the literature of the last fifty years is replete with examples of what has been considered the neurogenic type of Stokes-Adams attacks,¹⁷ such cases are seldom encountered in clinical practice. It is very likely that some of the reported cases were suffering from Stokes-Adams attacks because of pathologic lesions in the region of the vagus center in the medulla or in the pathway of the vagus nerve.^{18, 19} But even where polygraphic tracings accompany the reports of such patients whose records were obtained during syncope, it is impossible to discern the underlying cardiac mechanism, for as we have pointed out recently²⁰ transient periods of ventricular fibrillation may give the same type of polygraphic records as standstill of the heart, namely, a straight line indicating ineffectual contractions of the ventricles. Therefore, it is probable that many of the cases recorded in this polygraphic era

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THE STOKES-ADAMS SYNDROME. SOME CLINICAL
AND GRAPHIC OBSERVATIONS ON THE CARDIAC
MECHANISM UNDERLYING SYNCOPAL SEIZURES*

THE older clinicians^{1, 2, 3} were well aware of the fact that in many instances recurrent syncopal seizures associated with periods of unconsciousness and epileptiform convulsions (the so-called "Stokes-Adams seizures") occurred in the presence of "permanent bradycardia." But it was not until the comparatively recent introduction of the electrocardiographic methods for the study of the rhythms of the heart that it has been possible to appreciate the variety of cardiac irregularities underlying such attacks.

We now know, from an increasing number of carefully correlated observations, that syncopal seizures in patients in whom changes in the heart mechanism are responsible for the attacks may be due in the main to (a) a stoppage of the whole heart, that is, absence of both auricular and ventricular contractions from direct or reflex stimulation of the nodes of the heart through the

* The Stokes-Adams syndrome is a clinical condition characterized by recurrent attacks of unconsciousness, lasting from eight seconds to several minutes, associated with epileptiform convulsions and stertorous breathing ending in apnea. During such periods there is a collapse of the circulation with a drop in the blood pressure and absence of the pulse and heart sounds.

The term was coined by Huchard¹ who gives credit to both Stokes and Adams² for having described the clinical picture in the presence of bradycardia. Burnett⁴ and Pletnew,⁵ however, cite Morgagni⁶ as the first to have observed the phenomenon.

STOKES-ADAMS ATTACKS DUE TO INTERFERENCE WITH IMPULSE
FORMATION IN THE AURICULOVENTRICULAR NODE

The auriculoventricular node of the heart over which impulses from the auricles are transmitted to the ventricles is a very sensitive structure. Sudden interference with the circulation to this conduction system may result in a disruption of the normal sequence of events from the auricles to the ventricles. The ventricles may suddenly stop contracting before they assume an independent pace-maker of their own. In that event, the absence of cerebral circulation from a stoppage of the ventricles may result in a Stokes-Adams attack, the duration of which will be dependent upon the "pause" prior to the development of an idioventricular beat.

This "preautomatic pause" of the ventricles first observed experimentally by Erlanger and his associates^{13, 22} following crushing of the bundle of the dog's heart, is encountered in the clinic most commonly in patients with acute coronary vessel closure and in particular with closure of the artery which supplies the small vessels to the auriculoventricular node. Obviously, because of the very acute onset of such lesions, we have been unable to obtain electrocardiographic changes immediately after the vessel closure so that we cannot demonstrate that a "preautomatic pause" actually exists in human beings. However, the sequence of events which we have observed in these patients shortly after the initial lesion have been so like those noted in the experimental animal following crushing of the bundle, that we feel we are justified in assuming that the onset of these Stokes-Adams seizures were associated with a failure of the ventricles to initiate impulses of their own before the establishment of auriculoventricular dissociation.

Any Stokes-Adams seizures which appeared subsequently in these patients were during the presence of established auriculoventricular dissociation and were due to a marked slowing of the idioventricular rate.

In each of the three instances of this type of Stokes-Adams seizures which we studied during the past year, the heart rhythm preceding the seizures was known to be normal. Suddenly and

and considered as bradycardias of neurogenic origin would probably fall into the category of other types of Stokes-Adams attacks.

An example of standstill of the heart due to vagal inhibition in which the immediate cause of the excessive vagal tone responsible for bradycardia with Stokes-Adams seizures was believed to be primarily psychic in origin, was recently recorded by Wedd and Wilson.⁹ However, the dominant cardiac rhythm in their patient was one of nodal rhythm and it is very likely that the presence of this unusual basic rhythm had something to do with the syncopal attacks since it has been pointed out by Lewis²¹ that the influence of both vagi over rhythms emanating from the auriculoventricular node is powerful.

Enhanced vagal tone of psychic origin may influence the sinus node so as to cause standstill of the heart for a few seconds only, for the ventricles sooner or later initiate impulses of their own and in escaping, prevent the standstill of the heart of longer duration with the appearance of Stokes-Adams seizures. In the presence of some interference with impulse formation in the auriculoventricular node itself, this ability on the part of the ventricles to initiate their own rhythm is lacking as in the case described by Wedd and Wilson. Consequently, it seems to us that the Stokes-Adams seizures in their patient was the combined result of both vagal inhibition as well as some diseased process within the node itself.

Our own observations lead us to believe that enhanced vagal tone in itself can never result in standstill of the heart, that is, of both the auricles and the ventricles, unless there is some diseased process within its conduction mechanism. This accounts for the rarity of such cases; for enhanced vagal tone in itself is a common phenomenon in the clinic but the resulting bradycardia is invariably interrupted by an escape of the ventricles so as to prevent anemia of the brain.

The treatment and prevention of such syncopal attacks of neurogenic origin resolves itself in the adequate administration of atropine sulphate in doses of from 1/50 to 1/20 grain and repeated as often as is found necessary.

tion, and the subcutaneous injection of an adequate amount of adrenalin in doses of 1 cc. of the 1 : 1000 solution to stimulate the ventricular rate. This will prevent it from slowing so as to cause the anemia of the bulbar center resulting in the Stokes-Adams attacks.

In one woman who suffered from innumerable Stokes-Adams seizures following an acute coronary artery closure, we administered 8 cc. of adrenalin within two hours in order to maintain an adequate ventricular rate.

Each case, however, must be treated individually depending upon the frequency of the attacks and upon the severity of the shock due to the coronary vessel injury.

STOKES-ADAMS ATTACKS DUE TO A SLOWING OF THE VENTRICULAR RATE DURING ESTABLISHED AND CHRONIC AURICULO-VENTRICULAR DISSOCIATION

Of the last 27 consecutive patients with established auriculo-ventricular dissociation admitted to the Montefiore Hospital during the past eight years, seven gave a history of suffering from Stokes-Adams attacks. In five of these it was proved that the underlying cardiac mechanism responsible for these seizures was a slowing of the idioventricular rate to as low as 6 beats per minute.

In most patients in whom syncopal seizures are due to ventricular standstill, there may be absolutely no change in the ventricular rate prior to the onset of syncope. In others, alternate extra beats of the ventricles may disturb the basic rhythm. These in themselves, however, do not indicate whether the particular patient with heart block in whom they are observed is subject to syncopal attacks. For, if sufficient observations are made of all patients with permanent auriculoventricular dissociation, extrasystoles will be discovered at some time or other in each instance.

In a smaller group of such patients, the periods preceding syncopal attacks may be appreciated clinically, by a definite slowing of the ventricular rate, at first only one ventricular cycle being omitted and later several, until the ventricular rate becomes

without any premonitory signs, these patients collapsed. Two of them were in bed during this initial episode and were observed to experience epileptiform convulsions with foaming at the mouth and stertorous breathing accompanied by unconsciousness and incontinence of feces and urine. The exact duration of these initial seizures is unknown. When seen fifteen to thirty minutes after such an episode, their facial expressions were one of anguish. Their bodies were cold and moist. Their respirations were shallow and rapid. Their sensorium was cloudy. Their pulses were barely perceptible. There was a marked drop in the blood pressure which averaged 80 mm. of mercury systolic.

Each patient showed a low ventricular rate averaging 20 to 28 beats per minute with irregularly spaced ventricular contractions that varied markedly from minute to minute. In one patient the ventricular rate was as low as 14 beats per minute and repeated Stokes-Adams seizures were observed in her when the rate dropped to 6 beats per minute. No extraventricular contractions could be heard or felt so as to give a bigeminal rhythm at any time.

In all cases, the electrocardiograms revealed low voltage with marked intraventricular conduction disturbances, a marked cove-plane T wave in lead 3 and a positive large T wave in lead 1. The auricles beat regularly and averaged 90 beats per minute. The ventricular complexes were irregularly spaced and sometimes were upright in form while at other times they were downward.

In one patient the rhythm returned to normal forty-eight hours after the onset of the attacks but the patient died a few hours later in a severe paroxysm of pulmonary edema. The other two patients exhibited normal sinus rhythm four and six days respectively after the acute onset of their Stokes-Adams attacks and both are perfectly well today, having experienced no recurrent episodes of a similar nature since then.

The treatment of such patients consists of the application of warmth to the body to overcome the initial shock from the acute infarction of the heart, the intramuscular administration of caffeine-sodio-benzoate in $7\frac{1}{2}$ -grain doses to support the circula-

so that all the oscillations appearing after the fifth one may be registered electrocardiographically but cannot be heard at the apical region of the heart or felt at the pulse.

With a little practice it is easy to learn these events in their order of sequence clinically, so that it is possible to predict the increase in the frequency of the ventricular oscillations and their duration by the appearance of "silent" pauses interrupting the rhythm of the heart. As these pauses increase in number it is no longer necessary to resort to auscultation of the heart to determine such pauses because when the fingers become accustomed to the variations in the radial pulsations it is possible to tell the presence of these ventricular oscillations. For after the strong pulse, a pause is found to follow successively several progressively shorter and weaker pulse beats. While clinically to the casual observer this premonitory period would appear as a reduction in the ventricular rate, actually there is a definite increase in it if there is included the few heart sounds and palpable pulsations at the wrist that follow each basic ventricular complex, so that a heart rate of 30 beats would be increased very rapidly to one of fifty when a single premature beat appeared and to one of a higher rate when more appeared in rapid succession.

The recurring groups of ventricular oscillations which can neither be heard at the apical region of the heart or felt at the pulse are short runs of *ventricular fibrillation* (Fig. 45).

If such periods of ventricular fibrillation last for eight seconds but not for more than twelve seconds, then the patient's face assumes a deathly pallor, the eyes are shut, there is momentary unconsciousness followed by a sudden awakening, and a ruddiness of the face that coincides with a forceful beat of the heart.

Such short recurrent periods of unconsciousness of from eight to twelve seconds predicate and herald a typical major seizure of syncope. This may be accompanied by convulsive movements of various parts of the body, stertorous and irregular breathing, and incontinence of feces and urine. Spontaneous recovery is often associated with a clouding of memory that may persist for a whole day after the attack. Frequently,

so slow that the circulation to the cerebral centers is markedly diminished and syncope with convulsions sets in.

Most observations to date^{23, 24} with few exceptions²⁵ in which graphic evidences have been obtained in such patients, are in accord that if any change in the rhythm of the heart takes place prior to an attack, it is usually a *slowing* of the ventricular rate which precedes the major period of syncope. This slowing depends upon influences that affect the pace-maker of the ventricles.

THE VENTRICULAR RATE AND RHYTHM IN PATIENTS WITH STOKES-ADAMS ATTACKS DUE TO TRANSIENT SEIZURES OF VENTRICULAR FIBRILLATION

In patients with chronic auriculoventricular dissociation in whom Stokes-Adams attacks are due to transient periods of ventricular fibrillation the behavior of the ventricles preceding a period of syncope is totally different. There is usually an *acceleration* of the basic ventricular rate that takes place and this increase in the basic ventricular rate is brought about through a variety of mechanisms which we have already described in another communication.²⁶ But what is more important is that sooner or later during the acceleration of the ventricular rate, in the presence of complete heart block, prior to the onset of syncope, the rhythm is interrupted by *recurrent groups of ventricular extrasystoles*.

At first these alternate ventricular contractions appear singly or in groups of two or more after the main ventricular contraction of the idioventricular rhythm. At such times these extra beats can be heard at the apical region of the heart and felt at the pulse.

When these extraventricular beats increase in frequency, however, and observations are made of the movements of the galvanometer string at the same time that the heart sounds and pulses are studied clinically, it is noted that only the first four beats (at the most) following a basic ventricular complex can be heard at the apical region of the heart or felt at the pulse. These become progressively weaker in quality from beat to beat

THE USE OF ADRENALIN IN PREDICTING THE UNDERLYING CARDIAC MECHANISM RESPONSIBLE FOR SYNCOPAL SEIZURES IN PATIENTS WITH AURICULOVENTRICULAR DISSOCIATION

Now in studying the action of adrenalin on patients with auriculoventricular dissociation subject to syncopal seizures²⁰ we pointed out that there was a distinct difference between the effects of the drug on the rhythm of the heart of those in whom standstill of the ventricles was responsible for the Stokes-Adams attacks and those in whom the seizures were due to transient ventricular fibrillation.

Adrenalin was found to increase both the auricular and ventricular rates of the patients in whom syncopal seizures were due to standstill of the ventricles. In such patients, provided they responded to the drug, adrenalin was a life-saving measure when used intelligently. The increase in the ventricular rates were observed both preceding and during the Stokes-Adams attacks and were both regular and irregular in rhythm as may be gained from further studies carried out on such a patient.

Report of a Case.—C. T., a male, aged fifty-six years, was transferred to the Montefiore Hospital from the Presbyterian Hospital on October 10, 1931. His chief complaints on admission were recurrent attacks of syncope, occasional dizzy spells, and shortness of breath on exertion. His symptoms were of two years duration.

Previous Illness.—Ten years ago the patient began to complain for the first time of precordial pain. In July, 1929, he "fainted" on the street and when seen shortly after by a physician, his pulse was noted to be 16 beats per minute. He was admitted then to the Hospital for Joint Diseases where electrocardiograms confirmed the diagnosis of complete auriculoventricular dissociation with a ventricular rate of 36 beats per minute.

For the ensuing two years he was admitted to several institutions from each of which we were able to obtain the information that heart block was noted.

However, one hospital reports that on October 4, 1930, he showed normal sinus rhythm and in November, 1930, complete auriculoventricular dissociation had returned. During the following year he suffered several seizures of syncope, some of which were observed by physicians and it was established that the attacks were due to a marked slowing of the ventricular rate during dissociation of the auricles from the ventricles. On one of these occasions the ventricular rate was known to have been as low as 6 beats per minute. Because of this he was administered adrenalin during the syncopal attack and following recovery from this he was given 30 mg. of barium chloride three times a day.

Cheyne-Stokes breathing sets in and deep coma is not uncommon for sometimes as long as five hours after a major syncopal attack.

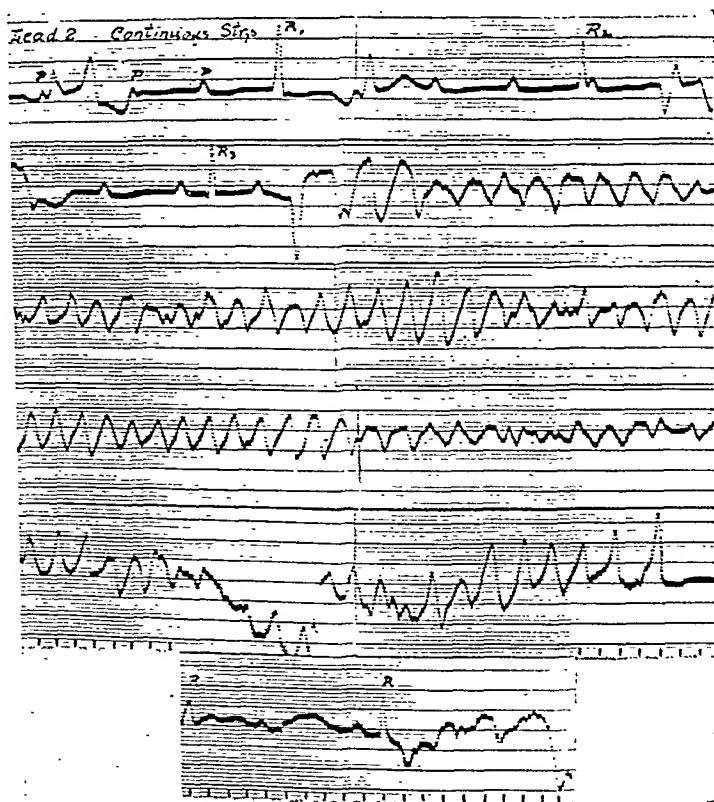


Fig. 45.—A continuous strip, lead 2 only, showing the period of ventricular fibrillation lasting twenty-six seconds. Note that this is preceded with an interruption of the basic ventricular rate by extrasystoles superimposed upon each other. The fibrillatory period is characterized by aberrant ventricular complexes without a definite base line and each one varying from the other in size, shape, and form. During such intervals there is a collapse of the circulation, a drop in the blood pressure, and absent pulses and heart sounds.

In short, the clinical manifestations of these seizures of transient ventricular fibrillation are identical with those produced by standstill of the ventricles as described above.

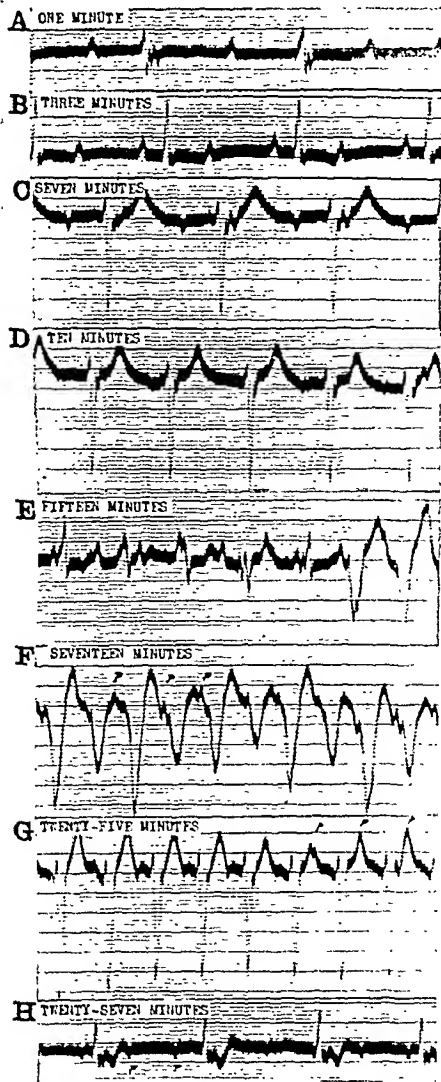


Fig. 46.—Lead 2 only. A series of successive electrocardiograms showing the action of adrenalin on a patient with heart block in whom it was established that the Stokes-Adams attacks were due to standstill of the ventricles.

complain of any symptoms except of consciousness of palpitation of the heart. Observations for several hours following the use of the drug on this occasion showed no further changes whatsoever.

Physical examination on admission to the Montefiore Hospital showed a poorly nourished individual whose memory was vague and who complained of shortness of breath. His lips were cyanotic. The superficial veins of the neck were distended. The right carotid artery was thickened and tortuous. The apical impulse of the heart was in the sixth intercostal space in the anterior axillary line. The apical heart sounds were barely audible, the first sound being partly replaced by a soft blowing systolic murmur. The aortic second sound was accentuated. The apical heart rate averaged 38 beats per minute and it was regular. The blood pressure was 260 mm. of mercury systolic and 60 mm. of mercury diastolic.

There were a few moist râles at the bases of both lungs posteriorly. The edge of the liver was palpable two fingerbreadths below the costal margin. There was moderate edema of the lower extremities.

An electrocardiogram taken on admission revealed complete auriculo-ventricular dissociation with a ventricular rate of 30 beats per minute and an auricular rate of 75 beats. All of the main ventricular deflections were notched and there was marked intraventricular conduction disturbance. The main ventricular complex in lead 2 was downward.

Course.—The patient was under observation at the Montefiore Hospital for a period of seven months. During this entire time he had only one severe syncopal attack which occurred at about midnight and was observed only by the nurse.

The effect of adrenalin on the rhythm of his heart was studied on five separate occasions, several weeks apart and at a time when it was well established that he had auriculoventricular dissociation with a ventricular rate that did not vary spontaneously more than from 8 to 12 beats per minute. The changes resulting in the heart rhythm following the use of adrenalin in him may be best appreciated from a description of the accompanying electrocardiograms.

At one time (Fig. 46) the subcutaneous administration of $\frac{1}{2}$ cc. of the 1/1000 solution of adrenalin was followed within one minute (A) by an increase of the ventricular rate to 33 beats per minute. Three minutes later (B) the rate was accelerated to 39 beats per minute and the ventricular complexes were now of a high voltage and upright as compared with those observed at seven minutes after the injection (C) which were of still higher voltage and downward when the rate of the ventricles was 46 beats per minute. At ten minutes (D) the rate had increased to 65 to be followed five minutes later (E) by a rate of 87 beats and with ventricular complexes of lower voltage and greater aberration. Two minutes after there suddenly appeared a tachysystole (F) of 120 beats per minute, all of which came through at the pulse. The ventricular complexes were now markedly widened and there was definite electrocardiographic alternation until eight minutes later when the ventricles slowed to 114 beats (G) and the complexes became narrower.

The basic ventricular rate did not return to its normal level until one-half hour after the beginning of the experiment. In the meantime the auricular rate increased from 75 beats to 120 beats and returned to its basic level about twenty minutes after the ventricles reached their original level.

During this tachysystole produced by adrenalin, the patient did not

Throughout this entire period no recurrent ventricular extrasystoles were noted.

On another occasion (Fig. 47) the same dose of adrenalin, injected subcutaneously, resulted in an increase in both the auricular and ventricular rates through a progressive shortening of the interventricular periods. At a time when the ventricular rate had been accelerated to 57 beats per minute, twelve minutes after the injection of the drug, a further increase in the ventricular rate took place through the interposition of a single extrasystole (A) which was of a totally different type from the basic ventricular complex. Following this interposed extra beat, a further increase of the ventricles to 88 beats per minute took place and within two minutes after there was a gradual slowing of the rate with restoration of the basic ventricular rhythm and a change of the main ventricular deflections as may be gained from the accompanying records (B).

Again, as previously, throughout this period of observation no recurrent groups of ventricular extrasystoles or periods of reexcitation were observed in this steplike acceleration of the ventricular rate. This time, however, the patient complained of some slight precordial pain in addition to consciousness of the rapid heart action.

The cardiac mechanism resulting from three further experiments of a similar nature on this patient in which adrenalin was injected either subcutaneously or intramuscularly revealed only a progressive increase in the basic ventricular rate. This acceleration lasted from fifteen to thirty minutes after the injection of the drug and was not followed clinically by any syncopal attacks.

No periods of *reexcitation* were observed to follow adrenalin in four other patients with auriculoventricular dissociation in whom similar studies were carried out and in whom it was known that the slowing of the ventricular rate was responsible for the Stokes-Adams attacks. In none of these cases was the acceleration of the ventricles as marked as the one whose records have just been described.

On the other hand, adrenalin in the same dose induced short runs of transient ventricular fibrillation with syncope in 2 patients in whom Stokes-Adams attacks were found to be due to ventricular fibrillation.²⁰

From a series of further studies which we have carried out on such patients during the past year, it was possible to demonstrate that the action of adrenalin was very variable from time to time in the same patient.

When such patients with Stokes-Adams seizures due to transient ventricular fibrillation were experiencing frequent re-

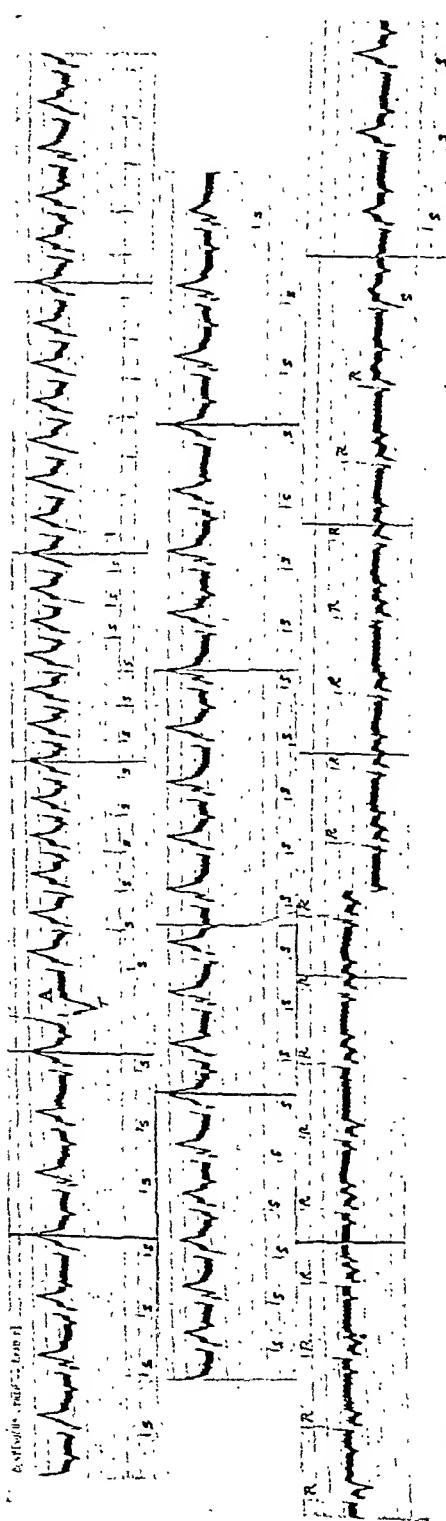


Fig. 47.—A continuous strip, lead 2 only, showing a progressive increase in the ventricular rate following the administration of adrenalin to a patient with complete heart block in whom it was established that the Stokes-Adams attacks were due to standstill of the ventricles. Note at A how the interpolation of a single extrasystole changes the rate from a low one to a high one.

rhythm was regular and uninterrupted by extraventricular contractions for several days prior to this study.

Before the injection of $\frac{1}{2}$ cc. of the 1 : 1000 solution of adrenalin, her ventricular rate was 38 beats per minute and regular with the auricles beating twice as fast (A). The ventricular complexes were of high voltage and all upright in form. Five minutes after the injection both the auricular and ventricular rates increased in frequency, the auricles averaging 125 beats per minute and the ventricles 70 beats, independent of the presence of extraventricular contractions. In the meantime (B) there developed a change from the apparent partial heart block to complete auriculoventricular dissociation and with this transition there appeared recurrent groups of ventricular complexes so superimposed upon each other as to increase the ventricular rate to over 300 beats per minute.

However, as we listened over the heart region and felt the pulse at the same time that these records were obtained electrocardiographically, we noted that only the first or second oscillation following a basic ventricular complex could be heard at the apex or felt at the wrist.

In short, these recurrent periods of ventricular oscillations following the injections of adrenalin resembled in every way clinically those seen spontaneously.

Such groups appeared between five and eighteen minutes after adrenalin and were accompanied by a sense of constriction within the chest and precordial pain but no syncopal attacks. All of these symptoms and signs disappeared gradually until at about thirty-five minutes after the beginning of this test both the auricular and ventricular rates returned to their original basic level.

Throughout the rest of the day no further acceleration of the ventricular rate was noted nor were there observed any recurrent premature ventricular beats either singly or in groups such as were described.

Similar studies with electrocardiographic controls were made on five other separate occasions on three different patients with Stokes-Adams attacks due to ventricular fibrillation, and invari-

current syncopal attacks, the use of adrenalin would increase the number of attacks. In the intervals when the attacks were absent or infrequent, the same dose of the drug that precipitated the syncopal seizures previously, now only resulted in the production of periods of reexcitation of the ventricles in addition to acceleration of the basic auricular and ventricular rates.

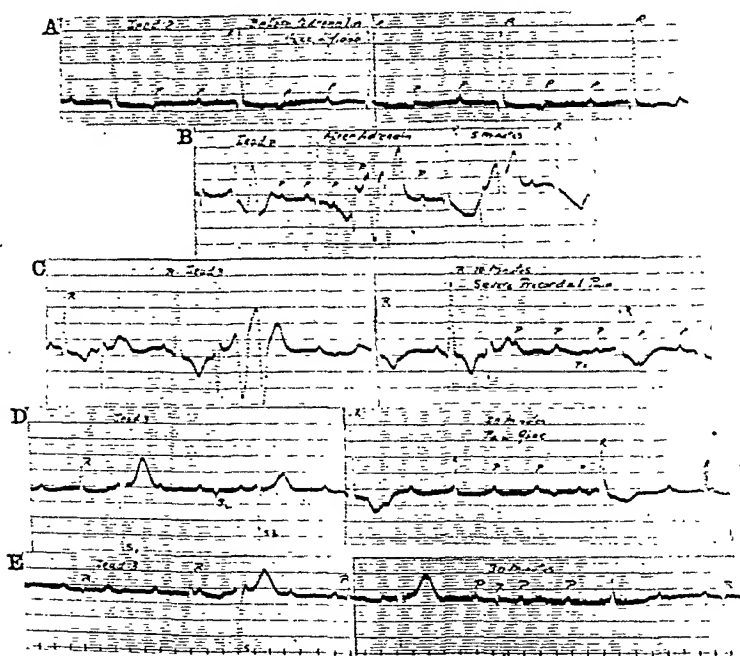


Fig. 48.—Successive electrocardiograms showing the action of adrenalin on a patient in whom it was established that the Stokes-Adams attacks were due to transient ventricular fibrillation. Note in particular the recurrent periods of excitation of the ventricles in these records as compared with Fig. 46.

An idea of the effects of adrenalin in such a patient whose Stokes-Adams seizures were known to be due to transient ventricular fibrillation, may be gained from a description of the following electrocardiograms (Fig. 48).

These records were obtained at a time when this patient was free from syncopal attacks for several weeks and after carefully controlled electrocardiograms revealed that her basic ventricular

These drugs are distinctly contraindicated in the Stokes-Adams seizures due to transient periods of ventricular fibrillation.

It is possible to differentiate the underlying cardiac mechanism responsible for Stokes-Adams seizures in patients with established auriculoventricular dissociation by the use of small doses of adrenalin during the free intervals. In patients in whom standstill of the ventricles is responsible for the syncopal attacks, adrenalin merely accelerates the basic idioventricular rate. In patients in whom the underlying mechanism responsible for syncope is the result of transient ventricular fibrillation, adrenalin produces short recurrent periods of ventricular excitation during the free intervals.

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ably the same results were obtained. Sometimes the periods of reexcitation of the ventricles did not appear until thirty minutes after the injection of adrenalin while at other times they appeared much sooner.

These observations, then, reveal a method for predicting the underlying mechanisms responsible for syncopal seizures in patients with Stokes-Adams attacks during established auriculoventricular dissociation. In those in whom standstill of the ventricles is the mechanism responsible for the attacks, adrenalin may merely accelerate the ventricular rate above that of the basic level. On the other hand, in those patients in whom ventricular fibrillation is the cause of the attacks, adrenalin produces recurrent periods of reexcitation of the ventricles.

Because of this action, as a therapeutic measure adrenalin is a life-saving drug in the former cases; in the latter it is contraindicated.

SUMMARY

Stokes-Adams seizures due to enhanced vagal tone of psychic origin are extremely rare. The treatment and prevention of such syncopal attacks of neurogenic origin resolves itself in the adequate use of atropine sulphate in doses of 1/50 to 1/20 grain and repeated as often as is found necessary.

Stokes-Adams attacks due to interference with impulse formation in the auriculoventricular node are as a rule due to acute coronary vessel closure. These may best be treated during the acute episode by the repeated administration of adrenalin intramuscularly. If the patients survive the acute coronary episode, the attacks disappear with the restoration of the normal sinus rhythm.

Adrenalin may likewise be used in the treatment of Stokes-Adams seizures due to a slowing of the ventricular rate during established and chronic auriculoventricular dissociation. In some of these patients barium chloride in doses of 30 mg. three times a day may raise the threshold of the idioventricular pace maker and prevent the onset of such seizures. Sometimes the combined use of barium and adrenalin is successful where barium itself may fail.



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for years of substernal burning before a typical angina attack occurs. The symptoms of epigastric and right upper quadrant pressure and pain, often with palpitation, occur chiefly after meals or after exertion.

There is a peculiar tendency to get these symptoms particularly if the exertion takes place after a meal as illustrated by the following case: A female, age fifty-eight years, with generalized arteriosclerosis complained of epigastric pressure occurring one hour after a meal but only if she walked. On resting after a meal there was no pressure.

The explanation of these early symptoms is unknown. Is it spasm of the esophagus or cardiospasm? Is it ischemia of the myocardium with reflex symptoms? Is it reflex gastric hypersecretion and spasm? Usually there are no significant electrocardiographic changes at this stage.

2. Probable Thrombosis of Small Branches.—The patients may have attacks of epigastric pressure or pain accompanied by nausea and vomiting. The symptoms may last a few minutes to a few hours and are often diagnosed as "acute indigestion." The electrocardiogram shows either no deviation from the normal or slight changes which are insufficient for the diagnosis of coronary artery disease.

3. Thrombosis of Large Coronary Artery Branches.—Here, without any or only very slight precordial pain, one may get very severe abdominal symptoms. In fact, so severe that Willius states "atypical angina pectoris may simulate every known acute surgical condition in the abdomen." The patients may present the picture of perforated peptic ulcer, acute pancreatitis, acute gallbladder disease, or intestinal obstruction. Levine reported in 1918 2 cases suggestive of an acute surgical abdominal condition who were operated on with subsequent exodus. At autopsy only coronary thrombosis was found. Many authors (Herrick, Gorham, Paullin, Faulkner, Willius, Osler) have described this error. Even Neusser, the great clinician, in his book "Angina Pectoris" cites the case of a female who was operated on for gallbladder disease and at the postmortem examination coronary thrombosis was found. Surgeons are confronted

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ABDOMINAL SYMPTOMS AND CORONARY ARTERY DISEASE

It is the purpose of this paper to discuss briefly certain clinical pictures in which (1) abdominal symptoms are presented by disease of the coronary arteries, (2) precordial symptoms are presented by organic abdominal diseases, and (3) combinations of the two. Of course, it will be necessary to mention certain functional disturbances which also give rise to such symptom complexes.

It should be emphasized at the outset that clinical symptomatology, particularly the symptom pain and its substitutes, may be tremendously varied depending on the reaction of the individual to his disease. Libman has emphasized the fact that atypical clinical pictures of disease and particularly abnormal radiations of pain occur chiefly in individuals who are hypersensitive. In the group under consideration we are dealing in most instances with patients with atypical reactions.

We will first discuss the symptoms of organic coronary artery disease. These symptoms may be grouped as follows: (1) The premonitory symptoms. (2) The symptoms of probable thrombosis of small branches. (3) The symptoms of thrombosis of large branches. (4) The sequelae of (1) and (2). (5) The reflex phenomena associated with (1) and (2). We will confine ourselves to the abdominal manifestations of coronary artery disease. We do not intend to discuss the typical syndromes such as pain on exertion or the precordial seizures.

1. **The Premonitory Stage.**—We may assume that sclerosis with some narrowing of the coronary vessels exists. Spasm may possibly be an additional factor. These patients often complain

2. Belching.—This is one of the most frequent symptoms in all stages of coronary artery disease. Apparently it is chiefly due to aerophagia. A few relevant paragraphs may be cited from the author's paper, "Some Clinical Features of Air Swallowing."

"There are aerophagics with organic gastro-intestinal, gallbladder, liver, and cardiovascular disease. These patients recall that epigastric pressure is often relieved in their normal state by belching. When, therefore, because of their disease, they feel epigastric pressure, discomfort or pain, possibly due to a reflex increase of the intragastric pressure, they swallow air, belch, and thus temporarily obtain a sense of relief. The constant repetition of this act soon becomes a habit or conditioned reflex and as such is a leading symptom well known to the physician. In fact, in some hyposensitive individuals, belching may be the only symptom of organic disease. In other words, belching may form the equivalent of the usual symptoms of disease of the coronary arteries, chronic gallbladder disease, or even peptic ulcer.

"An interesting group has been described particularly by Rieder under the title of 'Gastric Pneumatosis.' Here large quantities of air are swallowed and the gas remains trapped in the stomach. This is done unconsciously and usually, although not necessarily, with a meal.

"The symptoms in this condition are interesting. Frequently the patients are most uncomfortable after a meal, because of the great epigastric distention. At times this distention leads to the most distressing cardiac and respiratory symptoms. The older writers, when the respiration particularly was disturbed, called it 'asthma dyspepticorum' (Henoch). Shortness of breath after meals or exertion, even extreme dyspnea, has occurred. Various cardiac symptoms may arise. The mechanism of the cardiac symptoms may be explained by the elevation of the left diaphragm acting mechanically and the distention and cardio-spasm possibly acting reflexly. False angina pectoris, extrasystoles, and palpitation occur. Vaquez and Bordet actually produced extrasystoles in normal persons by inflating the stomach. Obviously the swallowing of large quantities of air by a

fairly frequently with this diagnostic problem. Is it coronary thrombosis or an acute surgical condition of the abdomen? The differential diagnosis is difficult but the following points are important in the establishment of the diagnosis of coronary thrombosis: (1) The overwhelming preponderance in males. (2) A careful history. (3) The electrocardiographic changes. (4) A falling blood pressure. (5) Leukocytosis (particularly without the Arneth shift to the left). (6) Precordial head zones. (7) Cyanosis. (8) Dyspnea. (9) Pulmonary signs. (10) Pulse irregularities. (11) A localized pericardial friction rub. (12) Evidence of arterial thromboses elsewhere (in the lower extremities or in the fundi). (13) The age. Inasmuch as the space is too short to go into these points, it can only be stated that such an intensive study is helpful in establishing the diagnosis.

4. *Sequelae*.—When the damage to the myocardium is extensive, cardiac insufficiency sets in. In one interesting group where possibly only the right coronary artery is occluded, the patients present the picture of isolated right heart failure. There is an enlarged liver, pain, and tenderness in the right upper quadrant, epigastric symptoms (pressure, pain, belching, nausea, and vomiting). Because of the absence of precordial symptoms and particularly dyspnea, and the right upper quadrant symptoms—even jaundice may supervene—these cases are often mistaken for gallbladder disease. In the remainder of this group there is typical cardiac insufficiency. The resultant venous stasis gives rise to a chronic gastritis with anorexia, nausea, epigastric burning, increased mucus, and hypochlorhydria. Abdominal distention and constipation accompany the chronic passive congestion of the intestines.

Before passing on to a discussion of the organic abdominal diseases with cardiac manifestations, certain symptoms deserve some comment.

1. *Epigastric Pressure and Pain*.—These common symptoms may be due to a nervous reflex causing increased intragastric pressure and increased tonus of the muscles of the abdominal wall. Of course, it is also possible that we are dealing with an atypical pain radiation from the precordial area.

ical. They may cause precordial pain, hiccough, dyspnea, and palpitation. A case was recently observed on the surgical service of a man fifty-five years old who suffered from a large gastric hemorrhage from a penetrating ulcer situated high on the lesser curvature. He had such severe precordial pain that the medical consultants unhesitatingly diagnosed coronary artery disease plus gastric ulcer. The postmortem examination did not show disease of the coronary arteries. Duodenal ulcer also, especially when it occurs in hyposensitive patients with atypical symptoms, with fair frequency gives precordial pain only.

The pains of chronic appendicitis at times radiate to the epigastric, precordial region, and the left shoulder. A patient was seen recently who complained of pain in the precordial region on walking. Pressure over his appendix produced pain at that site and simultaneously in the precordial area.

Renal pain occasionally radiates precordially and down the left arm. A few years ago a male patient was observed who had had many severe attacks of precordial pain considered angina pectoris. A typical ureteral colic then occurred and at the operation a calculus was removed from the left ureter. Since then the precordial symptoms have disappeared.

Before leaving this phase of the subject a comment should be made concerning the so-called "abdominal angina of Ortner." Ortner's disease, or, abdominal pain due to arteriosclerosis of the abdominal vessels, is frequently diagnosed whereas it is actually very rare. Usually one is dealing with an instance of coronary artery disease with an abdominal radiation of the pain, or, more frequently, with another abdominal disease. Recently a patient was observed on the surgical service who was sixty-five years old. He complained of severe attacks of abdominal pain and because of an advanced, generalized arteriosclerosis, Ortner's disease was diagnosed. Repeated radiographic examinations of the colon finally revealed a slight constriction in the midportion of the transverse colon. At the operation a small annular carcinoma was found at the site. Since the operation there has been a complete disappearance of the abdominal pains.

Finally there are certain functional disturbances which give

person with organic cardiac disease may be very harmful. This is particularly true in patients with true angina pectoris due to coronary artery disease.

"Leven, of Paris, has suggested that, if great distention can be demonstrated during an anginal attack, the stomach tube be passed. Although he reports good results, this seems a dangerous procedure.

"A study of the rôle of esophageal spasm and cardiospasm, and of gastric pneumatosis in the symptomatology of angina pectoris, especially in the functional cases, would doubtless prove of great value."

3. *Hiccough*.—When this occurs as a complication of an acute coronary thrombosis, it is a grave prognostic sign. It probably indicates either a reflex act or an epipericarditis occurring over an infarct with irritation of the diaphragm. The author observed 2 cases of acute coronary thrombosis with exodus in hiccoughs during the past year.

It is now necessary to discuss briefly the organic abdominal diseases which produce symptoms simulating disease of the coronary arteries. Foremost among these is disease of the gallbladder. The two diseases, gallbladder disease and coronary artery disease, have many features in common. For example, (1) age incidence, (2) the substernal symptoms, and (3) the gastric symptoms. Certain points favor the diagnosis of gallbladder disease. These are (1) the overwhelming incidence in females, (2) pain in the back, and (3) the right-sided character of the symptoms. Of course, it is well known that, in a fair percentage, possibly 20 per cent, the pains of gallbladder disease occur in the left lower chest and in the left upper quadrant of the abdomen. Furthermore, the fact must not be forgotten that frequently the two diseases coexist. Willius reported gallbladder disease in 26 per cent of one series of 96 proved cases of coronary artery disease.

Another important and frequent disease which simulates coronary artery disease is peptic ulcer. This is particularly true of gastric ulcer high on the lesser curvature. It is not generally known that the clinical picture of such high ulcers is often atyp-



rise to abdominal and precordial symptoms. Prominent among these is aerophagia which we have already discussed.

Another important cause is intestinal disturbance of a functional nature. There one encounters frequently abnormal gas accumulations under the left diaphragm, causing substernal pressure, heart burn, palpitation, dyspnea, and precordial pain. One can occasionally, by proper intestinal treatment, dispose of what seems to be coronary artery disease. It may be mentioned briefly that tobacco and coffee, or, nicotine and caffeine sensitivity, may cause a combination picture of precordial distress with palpitation and pylorospasm with ulcer-like symptoms. These symptoms may disappear completely with the discontinuance of these drugs. Although psychogenic clinical pictures are of the utmost importance, they will not be included in this discussion. It should be stated that such a diagnosis ought only be made after the most careful examinations and a long period of observation have excluded organic disease.

Summary.—1. Mild abdominal symptoms in individuals over the age of forty, often indicate disease of the coronary arteries.

2. Organic disease of the coronary arteries may wear a complete abdominal mask.

3. Thrombosis of the coronary arteries may present all the symptoms and signs of an acute surgical abdomen.

4. Certain abdominal diseases, particularly gallbladder disease, high gastric ulcer, duodenal ulcer, chronic appendicitis, and renal calculus, may project all or nearly all their symptoms into the chest.

5. The combination of organic abdominal and coronary artery disease is not unusual.

6. Aerophagia, intestinal hyperirritability, caffeine, and nicotine sensitivity may simulate coronary artery disease.

7. It is necessary often to investigate carefully every possible diagnostic point in establishing the diagnosis of organic coronary artery disease, when abdominal symptoms chiefly are presented.

patient and physician, insuring better cooperation on the part of the former and better understanding on the part of the latter. Informal consultations are frequent among members of the staff. Should a patient be unable to reappear at the clinic due to some acute illness whether related to his heart or not, the physician who is in charge of the patient is sent to his home at the suggestion of the Social Service Department. If hospitalization is required, he is given preference on the waiting list so that he can be admitted without delay.

The clinic population consists of 180 patients suffering from the usual rheumatic, hypertensive, and arteriosclerotic forms of heart disease. They have had frequent episodes of congestive failure, necessitating hospital admission with intervals of more or less improvement at home. Many have had auricular fibrillation for years. Experience has shown that prevention of infections, control of the apical rate and regulation of the water balance are the chief factors in the prevention of these acute episodes.

The problem of keeping a patient well digitalized when he is seen only weekly is far more difficult than when he is in the hospital, where apical rates and electrocardiograms can be obtained as often as is indicated. Moreover, our control over the clinic patient is much less complete; frequently full cooperation is not obtained. Patients at home frequently omit doses or take extra doses, and quite often may pass several days in succession without taking digitalis at all.

Our main indication for the use of digitalis has been the presence of auricular fibrillation, and it is the use of the drug in this arrhythmia which concerns us here. The value of digitalis in cardiac patients with a regular sinus rhythm is still uncertain, but a discussion of this point is beyond the scope of this paper. For accuracy in dosage we have used almost exclusively, pills of standardized digitalis leaf in several sizes; 0.05, 0.1, 0.2, 0.3 Gm. In cases in which for some reason the patient could not take pills, and it was necessary to administer a liquid preparation, a standardized tincture was used; and the dose ordered, not in drops, but in minims or cubic centimeters which the patient measured in a graduated minim glass.

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INTENSIVE AMBULATORY TREATMENT OF PATIENTS SUFFERING FROM ADVANCED CARDIAC INSUFFICIENCY

WHILE the treatment of the advanced cardiac patient has been fairly satisfactory in the hospital, that given outside has been much less effective. Such patients, treated in the usual clinic or office practice, must frequently be hospitalized for more intensive therapy. The object of this study was to see to what extent the approved methods of treatment carried out in the hospital could be successfully applied in the clinic. The principles followed in the management of these patients on the wards of the Montefiore Hospital during the past few years have been summarized by Hyman and Fenichel.^{1, 2} The aim of our follow-up clinic has been to enable the patient to lead a comfortable existence at home and to relieve the mental attitude of the hopeless invalid by delaying his readmission to the hospital as long as is possible without sacrificing his best interests. If a fair percentage of these individuals can be successfully treated as out-patients, and their inevitable readmission to the hospital be postponed, a considerable number of beds become available for others who need them. This is a social problem of great importance in view of the scarcity of institutions whose policy includes the care of the advanced cardiac patient.

Patients discharged from the hospital are therefore referred to the clinic, which is intimately coordinated with the hospital proper. Each is assigned to one of the staff physicians, who sees him at every visit, which is made by appointment. This arrangement brings about a more intimate relationship between

ing, when he is to omit digitalis for one day, and then commence with a smaller daily dose. He is then to report on the next clinic day. Many patients in this way learn to gauge exactly the required dose by steering between nausea and vomiting on one hand, and dyspnea and palpitation on the other. In this way patients have been kept digitalized without any cardiac failure for long periods, even for years, and have been seen medically only at intervals of one to eight weeks. It is obvious that the rapid method of digitalization is not feasible in these cases, as occasionally a patient may not reappear at the clinic for several weeks after digitalization is commenced; and even if he is seen in a week, dangerous toxic manifestations may appear within that interval.

The administration of digitalis and the maintenance of a low apical rate by no means constitute the entire problem. We have been greatly impressed by the disturbances in water metabolism as evidenced by water retention. The functional capacity of the heart is usually so greatly impaired that mere rest and digitalization are not sufficient to render the patient edema free. The water-logged tissues require additional assistance, and the judicious use of the proper diuretic supplies the necessary aid.

The success of diuretic therapy depends not only on the choice of diuretic, but also on our ability to induce the patient to adhere to a proper diet. The fact that he needs restricted fluid and salt intake requires no discussion. It is, however, not sufficient to tell a patient, "Don't drink much water," and "cut out salt." Experience has shown that poor results are often due to such ambiguity. The patient requires specific directions. How much fluid may he have daily? What foods contain the least salt? Most people fail to realize that many prepared foods, as bread, canned food, etc., contain large quantities of salt, and that the mere failure to add salt in the home preparation or at the table will not necessarily produce a salt-poor diet. They also overlook the fact that most foods contain water. Even the apparently obvious fact that coffee, soups, and orange juice consist chiefly of water must be emphasized. A patient may

Gold and De Graff have been especially interested in the digitalis treatment of ambulatory cardiac patients. In a series of articles^{3, 4, 5, 6} they emphasize the following points:

It is possible to digitalize a patient by giving repeated relatively small daily doses, and to keep him digitalized with exactly the same dose.⁵ The effective concentration needed to maintain the full therapeutic result is less than is required to produce full digitalization at the beginning.⁶ The elimination of digitalis does not occur at a fixed daily rate as was commonly believed,⁴ but varies with the amount present in the body; as the latter diminishes, the amount of digitalis excreted daily also diminishes.

Our experience has been in accord with these observations, and we have pursued the following methods in the clinic. The patient, after having been discharged from the hospital some time previously, and after having taken more or less digitalis in the interim, enters the clinic in auricular fibrillation with an elevated apical rate. Our object being to maintain a ventricular rate of about 80, a daily dose of digitalis of about 0.3 Gm. is prescribed; this should allow some accumulation during the next week. If the patient has not had digitalis for several weeks previously, the procedure is about the same, except that the initial daily dose is somewhat larger. Of course, the exact dose ordered for any individual varies with many factors; the ventricular rate, the grade of cardiac insufficiency, the degree of nervousness. The patient returns in a week. If necessary he is seen on intervening days at one of the other clinics in the hospital, but this visit is usually not required.

If the rate has fallen sufficiently, the daily dosage is reduced, and the patient seen weekly until the smallest quantity sufficient to maintain the optimum rate is found. Experience has shown that this dose is by no means fixed and cannot be arbitrarily stated in advance. Moreover, it frequently must be altered as signs of acute infection, increasing ventricular rate or symptoms of over-digitalization develop. Occasionally 0.4 Gm. or more is given daily if the rate persists, and no toxic manifestations appear. The patient is instructed to watch for nausea or vomit-

The diuretics used fall into four groups.

1. Mercurial: salyrgan.
2. Urea.
3. Acid-producing diuretics: ammonium chloride, ammonium nitrate.
4. Xanthine derivatives: theocine, theobromine, diuretin. —

Salyrgan (mersalyl) is the most spectacular of the diuretics, and has been much used by us. Its effects and the methods of its administration are well known, have been frequently discussed in the literature and need not be described here. The initial dose is $\frac{1}{2}$ cc.; in subsequent administration the dose may be increased to 2 cc. per injection. The effects begin in four to six hours and are usually over in twenty-four. Patients often comment about the increased urinary output. The edema often subsides, cough and dyspnea improve, and the enlarged liver becomes less painful.

The essential point in therapy is persistence. Even though no satisfactory response is obtained in the beginning, sooner or later, in most cases, results will be obtained. Salyrgan has proved a powerful weapon in the treatment of these advanced cardiac patients and while we would hesitate to say that it has prolonged life, it has certainly made it more tolerable for these people. The drug, however, presents certain obvious disadvantages. Renal insufficiency is a definite contraindication. For this reason it must not be given where the urine is of fixed specific gravity at a low concentration, or where there is nitrogen retention in the blood. If the retention is due to circulatory failure, as evidenced by a urine of high specific gravity, salyrgan may safely be administered. Albuminuria is no contraindication. The fear of severe toxic reaction is unjustified. Tarr and Jacobson⁷ have studied the results of 3000 injections of salyrgan given at the Montefiore Hospital. There were only two instances of mild stomatitis. Three cases of nerve paralysis occurred due to faulty intramuscular injection. In 30 cases which came to autopsy, only one showed lesions in the kidney suspicious of mercurialism. These observations are more noteworthy in view

honestly believe that he is observing a restricted fluid diet if he consumes only 2 glasses of water daily, but has 3 cups of coffee, a plate of soup, and 2 or 3 oranges in addition.

Furthermore, we must also realize that the natural craving for water may cause the patient to take much more than is ordered, and later to deny that fact to the physician. This has often been our experience, and explains the frequent failure to lose fluid even when there is apparently perfect cooperation. Every attempt is made during the patient's stay in the hospital to enlighten him fully on this subject. We have prepared "limited fluid and salt diet sheets" for distribution to our patients, who are to consume only what is on the sheet. Experience has shown that the total fluid content of the diet cannot be restricted to less than 1400 cc. except for very short periods (two to three days) at a time.

GENERAL INDICATIONS FOR THE USE OF DIURETICS

Edema.—This is often, but not always manifest. As is well known, a patient may retain as much as 15 to 20 pounds of fluid in his tissues without anasarca. Each patient is weighed at every clinic visit; fluctuations in weight are then usually due to gain or loss of retained water.

Congestive Symptoms.—Dyspnea and cough are frequently due to pulmonary congestion. The judicious administration of a diuretic, even though no manifest edema is present, will often relieve these symptoms. Then, too, pain and discomfort in the liver region due to engorgement of that organ can often be relieved in the same way.

Paroxysmal Nocturnal Dyspnea.—Through some unknown mechanism, fluid retention is an important factor in the production of these nocturnal attacks. The amount of retained fluid may be quite small; in fact 2 pounds increase in weight may be accompanied by attacks. Close observation of the patient for premonitory signs, such as oppression at night or increasing orthopnea, with timely administration of salyrgan may prevent these attacks of paroxysmal nocturnal dyspnea.

markedly delayed, and a real break in compensation may be averted for surprisingly long periods of time.

The acid-producing diuretics may be used, not only as adjuvants to urea and salyrgan, but independently, when the patient has no tolerance to the others or does not respond to them. These salts often enhance the action of salyrgan in cases where salyrgan alone does not produce marked diuresis. Of late we have been using ammonium nitrate in 40 per cent aqueous solution in individuals who for some reason could not take urea. The nitrates have long been known to produce diuresis; and Keith, Whelan, and Bannick,⁹ have shown that ammonium nitrate is especially efficient. Its action is produced in two ways. On absorption it splits into the ammonium and the nitrate radicals. The ammonium fraction is readily converted into urea which is excreted by the kidney. The nitrate concentration in the blood is increased by the other radical and 90 per cent is excreted by the kidney.

A great advantage of ammonium nitrate is that it does not have to be given in as large doses as urea (8 to 12 Gm. daily), so that it is much easier to take, and in a number of cases it is as effective as urea. In some people, indeed, it will produce a diuresis when urea will not. To patients who could not tolerate the taste of this drug we have tried giving it in chocolate-covered pills of 0.5 Gm. but the fact that 15 to 20 pills must be taken daily makes this form of administration troublesome. Of late we have discontinued the use of these pills.

Administered in any form care must, however, be exercised in the use of ammonium nitrate. Although we have not personally observed such a reaction in the clinic, methemoglobinemia has occurred in the hospital due to its continued use,¹⁰ so that it is not entirely without danger. We therefore allow frequent rest periods by prescribing 2 teaspoonfuls three times a day (10 Gm. daily) for five days a week, and having the patient omit it at the week end. Renal insufficiency with nitrogen retention, as in the case of salyrgan, is a contraindication. In spite of its limitations ammonium nitrate is a very efficient diuretic and

of the fact that many of the hearts and kidneys showed severe degenerative lesions and that the patients received many injections of salyrgan—in one case a total of at least 130 cc.

The fact that it must be given by injection is a disadvantage. Then there is the tendency to venous thromboses at the site of injection. Moreover, with repeated administrations it tends to lose its efficacy. Under these circumstances the injections must be stopped for a time, after which their effect is frequently restored.

While the action of salyrgan is usually very rapid and efficacious, its effects are quite transitory, and other diuretic measures are necessary to maintain a daily diuresis of satisfactory volume.

Urea is a very efficient diuretic over long periods of time. In this hospital we have used it in large doses for very long periods.⁸ Though not as powerful as salyrgan, it is an extremely useful adjuvant to it. Very frequently it will prevent the reaccumulation of fluid, once this has been removed by salyrgan. Then too, under clinic conditions where the patient is not seen for at least a week, it may be given as a "maintenance diuretic," filling the gaps between the clinic visits at which salyrgan is administered.

Urea has not been in general favor largely because of the fact that the doses usually used are far too small. The smallest dose we have found to be of any value is 45 Gm. daily, divided into three parts. The usual quantity prescribed is 70 Gm. a day, and occasionally more. The patient is given a prescription calling for 1 pound of urea crystals. This is to be dissolved in a quart of warm water and then cooled, making a 50 per cent solution. Three tablespoonfuls three times a day gives the patient 70 Gm. of urea. The mixture is taken after meals to lessen gastric irritation. The patient soon learns to tolerate the rather unpleasant ammoniacal taste, and may take the mixture uninterruptedly for months or even years without untoward effects. There may be a slight rise in the blood urea nitrogen, but except for minor skin eruptions we have never seen toxic symptoms. Under this régime the reaccumulation of fluid is either halted or

Date.	Apical rate.	Digitalis.
5/ 4/31.....	59	0.1 Gm.
5/25/31.....	100	0.1 "
7/ 6/31.....		0.1 "
9/28/31.....	80	0.1 "
10/19/31.....	80	0.1 "
11/ 2/31.....	92	0.1 "
11/30/31.....	110	0.1 "
1/ 4/32.....	120	0.1 "
1/25/32.....	96	0.1 "
3/ 7/32.....	60	0.1 "
3/28/32.....	76	0.1 "
5/ 9/32.....	77	0.1 "
6/27/32.....	78	0.1 "

Shortly after the last visit she was transferred to another clinic nearer her home.

This was one of our most difficult cases to handle, and the results were not entirely satisfactory. The patient had very little cardiac reserve, and without digitalis had a ventricular rate of 160. Intelligence was below normal and cooperation was poor. She frequently did not reappear until sent for by our social service. She often took or omitted digitalis as she saw fit. For this reason no attempt was made to give her larger doses for fear of toxic manifestations. In spite of this, her apical rate was kept fairly consistently below 100 for two years. For the last year she was kept well digitalized on daily doses of 0.1 Gm.

Case II.—I. W. This was a man aged fifty-four, suffering from arteriosclerosis, coronary artery sclerosis, auricular fibrillation, and arborization block. The complaints began in 1927 with dyspnea, orthopnea, and fatigue, soon followed by circulatory failure. There were three admissions to Montefiore Hospital between November, 1927, and March, 1930. Each time he was admitted in congestive failure, and after each stay in the hospital under diuretic and digitalis therapy he was discharged much improved.

Since 1927 he has been taking urea almost constantly, 70 Gm. daily; this amounts to about 50 pounds of urea a year, and in the five years he has been under observation 250 pounds, or more than his body weight. There has been some nitrogenous retention, but no toxic symptoms.

Blood urea nitrogen 48. Creatinine 2 (4/22/30).

Date	Weight.	Apical rate.	Digitalis.	Diuretics.
4/ 7/30.....	235	100		Urea, Salyrgan
4/14/30.....	231	112		"
4/28/30.....	237	110		" Salyrgan

many patients who are edema free under its influence will begin reaccumulating fluid immediately upon its withdrawal.

We have used ammonium chloride very little. Though at times it is very effective, it is much more irritating than the nitrate and has no advantages over it. The same may be said about calcium chloride.

The xanthine derivatives, as theocine, theobromine, and theobromine-sodium salicylate do not find a very important place in the treatment of these patients. We have tried them on many occasions, and while at times profuse diuresis may result from their administration, this is usually not the case. Even when good results are obtained, their effect is soon lost, and they cannot be used as maintenance diuretics. Though we realize their importance in other conditions, we are convinced that they are too unreliable to use as maintenance diuretics in advanced cardiac patients.

The following cases illustrate the principles just discussed.

Case I.—H. L., a woman aged forty-eight, was first seen by us on April 28, 1930, after six months treatment at Montefiore Hospital. Her diagnosis was chronic rheumatic cardiovalvular disease, mitral stenosis and insufficiency, auricular fibrillation, with congestion of the liver and lungs. There had been several previous admissions to other hospitals. A note from one of these stated, "The patient cannot remain compensated, and returns in a few days with acute decompensation." At Montefiore Hospital she was given digitalis and diuretics and was discharged improved. Her apical rate in the hospital had ranged from 74 to 90, after full digitalization.

Date.	Apical rate.	Digitalis.
5/19/30.....	140	No digitalis; sedatives.
5/26/30.....	160	$\frac{1}{2}$ cc.
6/16/30.....	160	0.2 Gm.
6/23/30.....	72	0.2 "
6/30/30.....	72	0.2 "
8/18/30.....	80	0.1 "
10/13/30.....	80	0.1 "
11/10/30.....	110	0.2 "
12/ 1/30.....	110	0.3 "
12/15/30.....	86	0.3 "
1/15/31.....	86	0.2 "
1/26/31.....	76	0.1 "
2/16/31.....	80	0.2 "
3/16/31.....	84	0.2 "

Date.	Weight.	Apical rate.	Digitalis.	Duretics.
12/21/31.....	215	80	0.1	Urea
12/28/31.....	216		0.1	"
1/25/32.....	216		0.1	"
2/29/32.....	220	80	0.1	" Salyrgan
3/ 7/32.....	219	72	0.1	"
4/ 4/31.....	220	78	None	"
5/ 2/32.....	229	86	0.2	" Salyrgan
5/ 9/32.....	220	76	0.2	" Salyrgan
5/16/32.....	216	70	0.2	" Salyrgan
5/23/32.....	217	78	0.2	"
7/11/32.....	219	68	0.2	"
7/25/32.....	217	76	0.2	"
9/19/32.....	215		0.2	"
10/17/32.....	215	70	0.2	"

This is one of our best cases. He is a man with advanced circulatory failure and always has more or less edema. He is very cooperative; he measures his fluid intake and restricts it to 800 cc. daily. The very high weights do not represent edema only. He is very obese and his weight without edema is probably over 200 pounds. For over two years he has been kept comfortable and practically always ambulatory with digitalis, urea, and salyrgan. He has taken 70 Gm. of urea daily almost continuously, and has had at least thirty-two injections of salyrgan during that period. The tendency to reaccumulate fluid is marked. An attempt to substitute ammonium chloride for urea on November 3, 1930, was followed by a marked diminution in the urinary output, marked increase in dyspnea, and a gain of 4 pounds in weight in three days. After another attempt to discontinue urea (April 27, 1931) there was again marked circulatory distress, with dyspnea and oliguria, although there was only a slight gain in weight. The response to salyrgan is usually very satisfactory. One injection often produces a loss of 6 to 8 pounds and occasionally much more. At times there is a gain in weight in spite of salyrgan. It is then not given for several weeks, when its effect is restored. As the table shows, he did not begin to do well on diuretics until he was also given digitalis. On diuretics alone his weight rose to 246 pounds (July 7, 1930). He was kept at home in bed for three weeks and was given digitalis, urea, and salyrgan. When he returned to the clinic he

Date.	Weight.	Apical rate.	Digitalis.	Diuretics.
5/ 5/30.....	234	110		Urea, Salyrgan
5/12/30.....	229	120		" Salyrgan
5/19/30.....	229	96		" "
6/ 2/30.....	236	90		" Salyrgan
6/16/30.....	236	84		" Salyrgan
6/30/30.....	241	90		" Salyrgan
7/ 7/30.....	246	76		" Salyrgan

At home in bed; 5 salyrgan injections till next visit (twenty days); Tr. digitalis 40 cc. from 7/18/ to 7/28.

Date.	Weight.	Apical rate.	Digitalis.	Diuretics.
7/28/30.....	225	80	0.3	Urea
8/ 4/30.....	224	92	0.3	"
8/11/30.....	224	86	0.3	"
8/25/30.....	226	82	0.3	"
9/29/30.....	227	90	0.3	" Salyrgan
10/20/30.....	227	90	0.3	" Salyrgan
10/23/30.....	224	93	0.3	" Salyrgan
10/27/30.....	216		0.3	" Salyrgan
11/ 3/30.....	220		0.3	Amm. chloride
11/ 6/30.....	224		0.3	Urea, Salyrgan
11/10/30.....	217		0.3	" Salyrgan
11/17/30.....	223		0.3	" Salyrgan
11/24/30.....	226	84	0.3	" Karrell diet
12/ 8/30.....	233	96	0.3	" Salyrgan
12/15/30.....	221	76	0.2	" Salyrgan
12/22/30.....	217	74	0.2	" Salyrgan
12/29/30.....	213	84	0.3	"
1/ 5/31.....	219	80	0.3	" Salyrgan
1/12/31.....	219	76	0.3	"
1/26/31.....	219	76	0.3	"
2/16/31.....	216	64	0.3	"
3/30/31.....	216	64	0.3	"
4/27/31.....	218	80	0.1	Discontinue urea
5/ 4/31.....	219	63	0.1	Urea
5/11/31.....	221	90	0.1	"
6/ 1/31.....	219	76	0.1	" Salyrgan
6/22/31.....	213	72	0.1	" Salyrgan
6/29/31.....	211	60	0.1	"
7/20/31.....	212	65	0.1	"
8/10/31.....		80	0.1	"
9/ 4/31.....	211	86	0.1	"
9/28/31.....	215	80	0.1	" Salyrgan
10/19/31.....	218	88	0.1	"
11/ 9/31.....	213	88	0.1	"
12/14/31.....	221	76	0.1	" Salyrgan

Date.	Apical rate.	Weight.	Digitalis.	Diuretics.
6/ 6/32.....	82	121	0.3	Salyrgan
6/13/32.....	106	118	0.3	
6/27/32.....	80	115	0.3	
6/30/32.....		120	0.3	Salyrgan
7/11/32.....	84	122	0.3	Salyrgan
7/18/32.....	90	124	0.3	Salyrgan
8/ 1/32.....	84	126	0.3	Salyrgan
8/ 8/32.....	84	122	0.3	Salyrgan
8/15/32.....	79	118	0.3	Salyrgan
8/22/32.....	80	114	0.3	
9/12/32.....	84	114	0.3	
10/ 3/32.....	112	117	0.3	
10/17/32.....	113	120	0.3	Salyrgan

This patient offered a very difficult therapeutic problem; edema had to be controlled, the apical rate had to be reduced and severe precordial pain had to be relieved.

The water retention was at first not marked; later, however, edema became quite pronounced. Salyrgan was given chiefly for the relief of dyspnea and cough with very good results, which do not appear in the table. Urea or ammonium nitrate could not be given on account of gastric symptoms. Theocine for a time seemed to have some effect.

Digitalization was not entirely satisfactory. Rather large daily doses were required without complete digitalization. Still larger doses could not be given on account of nausea and vomiting. During the last year we were able to keep her rate below 100.

She did very well until October 17, 1932. She had been out of the hospital fifteen months and felt quite comfortable. On October 18, 1932, she suffered a cerebral hemorrhage with right hemiplegia and was immediately admitted to the hospital. She became progressively worse and died October 29, 1932. Autopsy revealed the following essential findings: Healed rheumatic endocarditis of the mitral and aortic valves with mitral stenosis and insufficiency, aortic insufficiency; hypertrophy and dilatation of the heart; arteriosclerosis of the coronary arteries with almost complete obstruction of the anterior descending branch of the left coronary; acute infarct of the interventricular septum

had lost 21 pounds and felt perfectly well. On April 4, 1932, an attempt was made to discontinue digitalis. This was followed by a gain of 8 pounds in four weeks. For the past six months he has done exceptionally well, and has not required salyrgan at all. His minimum weight was 211 on February 4, 1931, and his present weight (October 17, 1932) is 215. The auricular fibrillation is no problem here. His rate has been kept consistently below 90 with the aid of digitalis.

Although the ultimate prognosis is of course poor, with this man's quiet, inactive life, and his excellent cooperation he can go on in this way for a long time.

Case III.—L. S., a female aged fifty, was first admitted to the Montefiore Hospital in January, 1929, with a diagnosis of chronic rheumatic heart disease, mitral stenosis and insufficiency, hypertension, angina pectoris, auricular fibrillation, and congestive failure of one year's duration. Under the usual digitalis and diuretic therapy, she improved sufficiently to be discharged on July 20, 1929. There were four subsequent readmissions to the hospital on account of congestive failure between that date and July 20, 1931. During the period between January 14, 1929, when she was first seen, and July 20, 1931 she spent about twenty-two months of the thirty in the hospital, the longest period at home being five months.

Date.	Apical rate.	Weight.	Digitalis.	Diuretics.
7/20/31.....	90	129	0.3	
8/10/31.....	140		0.3	Diuretin, 22 grains daily
8/24/31.....	110	133	0.3	
8/31/31.....	88	133	0.2	
9/14/31.....	96	135	0.2	
9/28/31.....	100	136	0.2	Salyrgan
10/ 5/31.....	104	131	0.3	Salyrgan
10/19/31.....	110	129	0.3	Theobromine, 15 grains daily
11/ 2/31.....	86	131	0.2	Salyrgan, Amm. nitrate
11/ 9/31.....	110	129	0.3	Theobromine, 15 grains daily
11/16/31.....	120	128	0.3	
11/30/31.....	110	128	0.3	
12/31/31.....		128	0.3	
1/ 4/32.....	96	126	0.3	
2/ 8/32.....	100	124	0.3	Salyrgan
2/29/32.....	86	119	0.3	
3/21/32.....	82	120	0.2	
4/ 4/32.....	82	122	0.2	Salyrgan
4/25/32.....	88	117	0.2	
5/ 9/32.....	87	120	0.2	
5/23/32.....	90	118	0.3	Salyrgan

At first appearance it would seem that no appreciable loss of weight was caused by salyrgan. It must be realized, however, that the patient was not seen until a week or more after the injection, long after its effect had worn off, and the patient had had time to reaccumulate fluid. Our indications for injection of salyrgan in this patient were increased dyspnea, and increased discomfort in the liver region. Invariably, he felt much better after the injection. Moreover, this patient weighed himself each morning on a scale at home, and recorded his weight in a notebook. This record usually showed a loss of 4 to 5 pounds the day following the injection, and a slow gain to the original weight during the next week or two. Discontinuance of urea immediately caused aggravation of the symptoms.

During the year he was followed in the clinic he was prevented from reaccumulating fluid and his last weight was about the same as a year before. We feel certain that discontinuing urea would have been followed by a rapid gain in weight necessitating readmission to the hospital.

SUMMARY

An attempt has been made to treat ambulatory out-patients suffering from advanced cardiac disease, on the same principles as they are treated while in the hospital. Intensive therapy was found possible and effective.

For guidance we use the easily obtained objective signs, the weight and the apical rate, though the subjective symptoms, cough, pain in the liver region, paroxysmal nocturnal dyspnea, and its forerunners, nocturnal oppression, are important when the amount of retained water is not manifest.

Under clinic conditions, the rapid method of digitalization is impossible. The patients are digitalized by giving relatively small daily doses, sufficient to allow accumulation as shown by a graduated reduction in the ventricular rate. In the maintenance of its effect, it is stressed that no fixed daily dose of digitalis can be used. The so-called "maintenance dose," based on a fixed daily excretion is a myth. Constant observation of the

and anterior wall of the left ventricle; chronic passive congestion of the liver and spleen, edema of the lungs; the brain was not examined.

It is worthy of note that her final admission to the hospital was not for congestive failure, but for a progression of the basic pathologic lesions.

Case IV.—H. L., a male aged thirty-eight, was first admitted to the hospital on March 6, 1929, with a diagnosis of chronic rheumatic cardiovalvular disease, mitral stenosis, and insufficiency, aortic insufficiency and hypertension. His blood pressure was 210/120. There was marked circulatory failure with extreme hepatic enlargement. His weight on admission was 155 pounds. He improved rapidly, but was kept in the hospital for two years chiefly for economic reasons. He was discharged on April 14, 1931, much improved, weighing 143 pounds (without clothes).

Date.	Weight.	Diuretics.	
5/ 4/31.....	151	Urea	
5/18/31.....	148	"	
6/29/31.....	145	"	
7/13/31.....	145	"	
8/ 3/31.....	143	"	
8/17/31.....	143	"	
9/28/31.....	145	"	
10/12/31.....	145	"	Salyrgan
11/12/31.....	148	"	
12/ 7/31.....	149	"	
1/11/32.....	150	Diuretin and salyrgan	
1/25/32.....	150	Urea	Salyrgan
2/ 1/32.....	147	"	
2/29/32.....	149	"	Salyrgan
3/14/32.....	152	"	Salyrgan
4/ 4/32.....	149	"	Salyrgan
4/18/32.....	149	"	Salyrgan
4/25/32.....	145	"	
5/ 2/32.....	150	"	Salyrgan
5/23/32.....	147	"	
6/ 6/32.....	151	"	Salyrgan
6/20/32.....	149	"	Salyrgan
7/11/32.....	146	"	Salyrgan
8/22/32.....	150	"	Salyrgan
8/29/32.....	151	"	Salyrgan
9/12/32.....	147	"	Salyrgan
9/18/32.....	154	"	Salyrgan
9/26/32.....	153	Amm. nitrate	Salyrgan
10/ 3/32.....	153	Urea	Salyrgan

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ventricular rate, with regulation of the dose accordingly, is the only logical method of maintaining digitalization.

Sedatives are of great importance in treatment; they often reduce the rate without digitalis.

Of equal importance with the lowering of the apical rate is the maintenance of the water balance. This is accomplished by

1. The elimination of retained fluid by salyrgan.

2. The maintenance of diuresis sufficient to counteract the inevitable retention, chiefly by the use of diet, urea, and ammonium nitrate. The importance of specific instructions to the patient in restriction of water and salt intake is emphasized.

It cannot be stressed too strongly that the chief factor in the success of our treatment is infinite patience and persistence. One must not be discouraged if the patient does not respond immediately. It must be remembered that the handicaps are great. Cooperation cannot be ideal in dealing with patients who are lost sight of for relatively long periods of time. Then, too, we must remember that we are dealing with advanced cardiac lesions; and that our treatment has no effect on the basic pathologic processes. Ambulatory treatment is carried on only as long as the best interests of the patient do not require hospitalization. No attempt is made to keep a patient out of the hospital who really needs hospitalization.

Even with all of these limitations, a large number of patients are kept comfortable in the ambulatory state. The number of readmissions to the hospital in a group attending the clinic is much less than that in a similar group who do not. Under this regime life is made tolerable to them. They lose the attitude of the hopeless cripple, and acquire a new optimistic outlook on life.

Four cases illustrating the foregoing principles have been presented and those selected were fairly typical examples. All patients will not respond as well as these; on the other hand, many will show a much better response.

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The patient's previous history gives us the following data: She has been a resident of the United States for twenty-five years, during twenty-one of which she has been married. She is a para five, gravida five, and has had no miscarriages. Her menstrual history is negative. Her medical record evinces no history of scarlet fever, diphtheria, or rheumatic fever. In her surgical history, we note that she was operated for some ovarian condition immediately after marriage.

Thirteen years ago the patient had her first attack of pain in the right loin radiating downward into the groin. After the administration of morphine

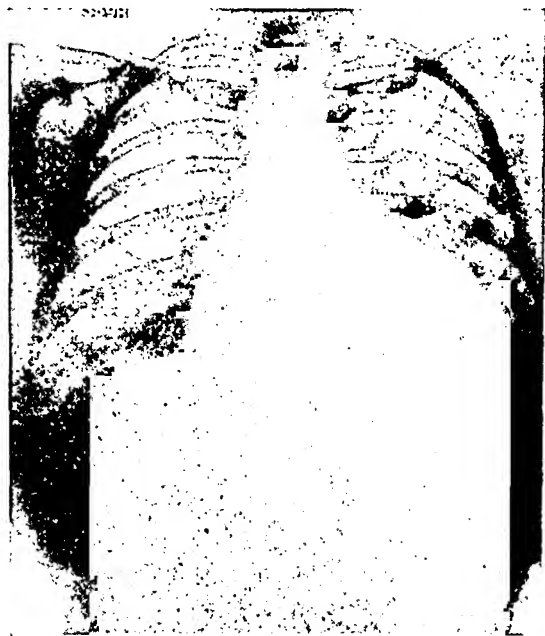


Fig. 49.—Marked increase in the transverse diameter due to enlargement of the left ventricle. There is some dilatation of the left auricle.

she passed a stone, and the attack was relieved. Similar attacks occurred every four or five months, always with an identical course. Her last attack occurred six years ago, at which time she was admitted to a hospital for operation. However, she was considered a poor risk which, in conjunction with the fact that she passed a stone and found her symptoms relieved, led to a decision not to operate. Instead, the patient was kept in the hospital for a period of four weeks while she underwent treatment for hypertension. In addition to the above, but separate therefrom, Mrs. Y. E. has had three attacks of frank hematuria. None of these was associated with pain or the passage of stones. During the past five or six years, she has been annoyed by polyuria and nocturia.

CLINIC OF DRS. ARTHUR WEISS, ALEXANDER GROSS-
MAN AND MARCUS A. FEINSTEIN

BETH ISRAEL HOSPITAL

HYPERTENSION: THREE PROBLEMS IN DIAGNOSIS

FOR a long time after Bright noticed the presence in renal disease of cardiac enlargement and rapid pulse, the conception prevailed that "without renal disease no hypertension." It is now generally accepted, however, that there are extravascular, vascular, and renal causes of hypertension.

Among the various forms of hypertension, we recognize cerebral hypertension (Kahler), hypertension accompanying an adenoma of the adrenal cortex, hypertension in conjunction with a basophil adenoma of the pituitary (Cushing syndrome), and, in the vascular group, there is hypertension in conjunction with arteriosclerosis. In addition to these, there is a much larger group comprising cases of essential or arteriolar hypertension, which in turn may be classified into two groups, namely, red or angiopathic hypertension and pale or angiospastic hypertension. Finally, there are cases where the hypertension is secondary to renal disease, such as glomerulonephritis.

In our clinic this morning we are presenting 3 cases of hypertension for diagnostic classification. The cases are from the Medical Service of Dr. I. W. Held, and Dr. Weiss will present the first patient, Dr. Grossman the second, and Dr. Feinstein the third case.

Case I.—Mrs. Y. E., age thirty-nine, was admitted to Dr. Held's service with the following chief complaints: A squeezing pain over the region of the heart accompanied by a choking sensation, dull pain in the right upper quadrant, shortness of breath, and a swelling of both lower extremities. All of these complaints have existed for ten days.

The family history yields nothing indicative of hypertension, nephritis, heart disease, diabetes, or insanity.

during which she has remained in bed, she has experienced several recurrences of mild precordial pain.

Physical Examination.—Admitted to the hospital, the patient presents a picture of a middle-aged, well-nourished white housewife, appearing pale and acutely ill. She is markedly orthopneic, the veins of her neck showing marked distention. Percussion of the thorax yields slight dulness at the right base. The heart apex beat is 14 cm. from the left of the sternum in the sixth interspace. A loud gallop rhythm is audible over the entire precordium. Her liver is enlarged and tender three to four fingerbreadths below the costal margin. Her extremities show a pitting, pretibial edema. The reflexes are normal. Her blood pressure is 248/178, pulse 100, temperature 100, venous pressure 22 cm., spinal pressure, 340; with withdrawal of 5 cc., 320; with withdrawal of 15 cc., 220.

x-Ray examination of the chest shows no lesions of either lung or pleura. Her heart is characterized by a marked increase in the transverse diameter due to enlargement of the left ventricle. There is some dilatation of the left auricle.

The laboratory findings are:

Urinalysis.—Her urine has a specific gravity of 1.004 to 1.014 and contains albumin 1 to 3 plus, and occasional red and moderate white blood cells.

Blood Count.—Red blood cells, 4,200,000; Sahli, 81; leukocytes, 10,200 with St., 1 per cent; S., 74 per cent; lymphocytes, 23 per cent, and monocytes, 2 per cent. Sedimentation test, 7 mm. in forty-five minutes.

Blood Chemistry.—Glucose, 84 mgm.; nonprotein nitrogen, 28; creatinine, 1.4; cholesterol, 173; uric acid, 3.7; chlorides, 470; indican, 0.17; total proteins, 5.6; albumin, 2.8 with albumin-globulin ratio—1.

Eye Examination.—An examination of the fundus shows marked hypertensive retinopathy in the right; to a lesser extent in the left.

The picture this patient presents is clearly one of cardiac decompensation, but has she acute coronary disease? Although the location and radiation of her pain may be considered typical, we feel that coronary thrombosis is not its underlying cause because she has a negligible temperature reaction, no leukocytic change of note, and a normal sedimentation rate. We have never seen a case of acute coronary artery disease with a normal sedimentation rate. Moreover, were the gallop rhythm due to coronary thrombosis one would expect a marked drop in blood pressure. We believe that the cardiac pain is due to decompensation and that the cause of the decompensation is an excessive hypertension that has endured for at least eleven years. The next problem is, of course, to determine, if possible, the cause of her hypertension. Had she an essential hypertension prior

Eleven years ago, when the patient visited a physician during the ninth month of pregnancy and complained of dizziness, headache, and swelling of the legs, he found her tension to be 185 and refused to deliver her, believing that she suffered from kidney trouble. Another physician was retained and patient was delivered of a normal child at term, experiencing no untoward symptoms. Since that time, however, she has complained frequently of frontal headaches, dizziness, blurring and spots before the eyes. During the last three years she has experienced occasional pains in the right loin, radiating downward into the leg. Her tension during the last two years has been about 240. She had



Fig. 50.—Stones in both kidneys, some hydronephrotic enlargement of left kidney pelvis.

had no puffiness of the eyelids and her ankles have become swollen only on rare occasions, at night, the swelling disappearing by morning.

In spite of her complaints the patient has always managed to be up and about and do her housework, except for occasional short rest periods called for by her dizziness and a feeling of faintness.

Ten days prior to admission, while engaged in household pursuits, she experienced a squeezing pain over the precordium which radiated upward into the neck. With this, there was a choking sensation and a dull pain in the right upper quadrant. She was not nauseous and did not vomit, but felt cold and perspired. She was helped to her room, where she improved within half an hour, but was too weak to leave her bed. In the ten days that have elapsed,

pensates, one may expect disturbances in rhythm such as auricular fibrillation, whereas when the heart fails in a case of renal hypertension there occur changes in contractility such as pulsus alternans and gallop rhythm.

Against the possibility that this patient is terminating as a case of malignant nephrosclerosis is the fact that she has improved and is improving under digitalis therapy. The progress of malignant nephrosclerosis cannot be halted; it is constant and ends always in uremia.

It is possible that we are dealing with a case of hypertension secondary to an old glomerulonephritis, but the patient gives no history of ever having had an acute glomerulonephritis. This alone, however, would be no criterion because the symptoms of such an acute attack may be so minor as to escape the patient's attention and give one a negative history. However, when acute glomerulonephritis progresses into the chronic state and gives rise to hypertension and an episode of nitrogen retention such as this patient had five or six years ago, there is little likelihood of a state of regression. In this case we find that the patient has had periods of renal failure with evidence of circulatory failure broken by periods of marked improvement. So we believe that an old glomerulonephritis is not the cause of this patient's hypertension.

The third possibility mentioned above was that Mrs. Y. E.'s hypertension might be due to hydronephrotic contracted kidneys. We feel that this most probably describes our patient. We know that there have been stones in both kidneys for at least eleven years. Acute obstruction can lead to rapidly progressing uremia, but with relief to the acute obstruction, azotemia, and hypertension will revert to normal. With a history of intermittent obstruction, a definite amount of kidney insult is to be expected. Constant repetition of this must finally result in a persistent hypertension. Although we realize fully the danger of subjecting this patient to surgical intervention, we know that the patient has a condition that will grow progressively worse unless something radical is done for her. We have concluded that the kidney stones are of sufficiently great moment to war-

to her nephrolithiasis? Is she terminating as a case of nephrosclerosis? Or, is she a case of renal hypertension, the hypertension being secondary to an old glomerulonephritis, complicated by nephrolithiasis? Or, may this not be a case of hypertension due to hydronephrotic contracted kidneys?

Six years ago the patient had, as yet, demonstrated no signs of either cardiac or renal insufficiency. Now, at this admission, her picture is definitely that of a hypertensive heart that has begun to fail. We know her condition six years ago from the records of the hospital where she sojourned at that time. She was admitted with a diagnosis of nephrolithiasis but in view of her obesity and hypertension operation was not performed. With bed rest and sedatives, her tension promptly dropped and stayed down for some time. Anti-obesity régime with oral thyroid resulted in a loss in weight of 22 pounds. An x-ray examination at that time showed small dendritic calculi in the right kidney and a small calculus in the left kidney. A blood chemistry examination showed: Urea N, -14 mg.; nonprotein nitrogen, -28 mg.; uric acid, -2.3 ; and creatinine, -1.3 . Evidently six years ago the patient had not as yet demonstrated signs of either cardiac or renal insufficiency.

If the patient's condition is one of essential hypertension with resultant decompensation, then her essential hypertension must have started when she was twenty-five or twenty-six years of age. Experience teaches us, however, that cases of this type usually terminate very quickly. Therefore, the eleven years' known history of hypertension is a finding against a diagnosis of essential hypertension. To the improbability of essential hypertension because of her youth, we may join the factors of a fixed specific gravity and hypertensive retinopathy. The fact that the blood pressure has remained high in spite of decompensation also militates against this diagnosis, even though we admit that an attack of circulatory failure *per se* may speak in favor of such a diagnosis. Gallop rhythm such as is heard in this patient is known to occur in both the renal and extrarenal forms of hypertension. It was Neusser who first called attention to the fact that when a case of hypertension of vascular origin decom-

increase of transverse and long diameters of heart due to left ventricle enlargement—aorta is sclerotic but not dilated.

Eye Examination—(Dr. Slomka)—10/22/32.

Right: Media clear, disk edematous, outline indistinct. Several large and small (albuminuric) whitish patches and retinal hemorrhages scattered all over fundus. In the macular region much darker in color. Several small white patches.

Left: Disk partially covered nasally by overhanging edematous retina. Entire nasal side-retina is edematous with marked venous thrombosis and retinal hemorrhages. In macula there is large stellate figure. There are also large and small exudates.

Diagnosis: Albuminuric retinitis—advanced stage.

The patient became progressively worse, twitchings occurred, Cheyne-Stokes breathing, and the psychic disturbances became so marked that she had to be restrained. Her nonprotein nitrogen rose to 200 mg., creatinine, 7.5 mg. On December 4, 1932, Dr. Slomka reexamined the eyegrounds and his report follows: Fundi show disks pale—left more than the right; numerous retinal hemorrhages and exudate present. No edema of disk or retina as seen upon previous examination.

Despite the institution of vigorous therapy, she went downhill rapidly and died on December 6, 1932, about six weeks after entering the hospital.

The outstanding clinical symptoms of severe headache, vomiting, hypertension plus the nitrogenous retention in the blood, present the unmistakable picture of uremia. The problem that confronts us, is what is the most probable pathologic picture of the decompensated kidney. Is it a primary kidney (vascular with secondary glomerular changes) or a secondary contracted kidney (chronic glomerulonephritis)? It is important from a prognostic standpoint, whereas from the standpoint of therapeutics, the end-stage of a primary or secondary kidney is not amenable to treatment. The outcome is fatal in both. But, in the clinic, it is essential to differentiate the two because, when renal failure develops in the course of malignant nephrosclerosis it is rapid, progressive, and relentless. In chronic glomerulonephritis definite remissions occur, uremic symptoms develop, and the patient might recover temporarily. In malignant nephrosclerosis once uremic symptoms set in, there are no remissions, the downward progress is so rapid and severe that it is justifiably called the most malignant of all renal diseases.

Pathologically, when we speak of primary kidney, vascular renal disease in hypertension, we refer to:

rant an attempt at their removal. Therefore, we are recommending the removal of the stones on the left side, where the hydronephrosis is greater. We hope this will improve the function of the left kidney as well as remove a focus of possible harm to the right kidney. Glucose should be given intravenously before the operation and the possible necessity of a transfusion should be kept in mind.

Case II.—The association of neuro-retinitis with malignant nephrosclerosis is well known. A case of malignant nephrosclerosis is now presented which lacked these necessary and essential eye findings.

R. K., a Jewish housewife, fifty-five years old, entered the hospital on October 20, 1932. She complained of headache, vomiting, dizziness, general weakness. Her family history was irrelevant. Her past history was essentially negative, except for frequent sore throats. She had been married thirty-eight years, had two children living and well. She had never been operated upon. She had been well until three years ago, when she developed dizziness and headaches. Her local doctor told her that she had a high blood pressure. In September, 1931, she was told her blood pressure was 270. She felt perfectly well until October 1, 1932, three weeks prior to her hospital admission, when her headaches became very severe and lasted all day. She vomited after each meal. She felt very dizzy and drowsy and grew progressively weaker. Progressive loss of vision occurred during these three weeks. Additional history was furnished by her daughter who told us that her mother had been treated for syphilis.

Physical Examination.—The patient was a middle-aged woman, not dyspneic or cyanotic, but looked chronically ill. Her complexion was sallow. There was no jaundice, no petechial or purpuric spots. The pupils were regular and reacted to light and accommodation. The lungs were negative to percussion and auscultation. The heart was slightly enlarged; the apex beat 3 cm. outside of the midclavicular line in the sixth space. Sounds were of fair quality and no murmurs were heard. The second aortic was loud and accentuated. Blood pressure was systolic 270 and diastolic 150. Abdomen was negative. Reflexes were exaggerated. There was no edema. Venous pressure was 7.5 mg. of water.

Laboratory Findings.—*Blood count* showed 3,000,000 to 2,500,000 red cells; hemoglobin, 62 to 52. *Blood Wassermann* on one examination was 2 plus, and on another negative. *Cerebrospinal Wassermann* was negative. *Blood chemistry*, total proteins 7.20; albumin, 4.32; globulin, 2.88; nonprotein nitrogen, 85 to 120; uric acid, 8; calcium, 9.2; indican, 2.56 mg. per 100 cc. (plasma).

Urinalysis.—Thirty-one urine examinations showed specific gravity varying from 1.005 to 1.012. Albumin 3 plus. Sugar negative. Examination of sediment showed occasional casts and white cells and on four occasions 6 to 10 red blood cells per field.

x-Ray of Chest: Lungs normal except for high degree of vascularization,

developed slowly, the renal changes were those of simple sclerotic atrophy (arteriolosclerotic contracted kidney). They found the rapidly developing uremias were associated with the more severe changes of malignant nephrosclerosis. Shapiro³ reported 36 cases of nephrosclerosis with uremia; in only one had the uremia been induced by simple progressive shrinking of the substance of the kidney until it was incompatible with life. In this one case particularly, every glomerulus was partly or completely hyalinized. Four of Shapiro's cases showed partial kidney atrophy (35 per cent of glomeruli were partly or completely fibrosed); passive renal congestion due to cardiac failure caused uremia. The majority of the cases ending in uremia, 31 of 36 did not show enough renal atrophy or enough passive congestion to account for renal failure. Twenty-three of the cases answered Fahr's classic description of malignant nephrosclerosis. In a series of 58 cases reported by Klemperer and Otani⁴ where deaths from different types of renal insufficiency were observed by the authors, 17 of these succumbed to malignant nephrosclerosis, 7 to benign decompensated sclerosis (Fahr). The differential clinical picture is one of degree and rapidity. The entire clinical course in the primary contracted kidney generally lasts longer and is less severe; these patients may remain for years in the stage of compensated impairment of renal function with diminished concentrating ability but normal blood chemistry. Renal failure sets in sooner and progresses unremittingly in the malignant nephrosclerotic. In the 16 cases reported by Klemperer and Otani the patient survived thirty-two days after renal inefficiency set in. Shapiro's 23 cases averaged five to six weeks. They may last a year, after renal insufficiency sets in, rarely longer.

The pathologic picture of malignant nephrosclerosis in contradistinction to group 2, reveals—a kidney not generally shrunk with diffuse flat granulations, characteristic ecchymoses due to severe vascular lesions. Microscopically, one sees narrowing of interlobular arteries due to cellular intimal proliferation, plus necrosis of vasa afferentia, collapse of glomerular capillaries. There is an extreme narrowing of the vascular bed

1. Arteriosclerotic kidney (benign nephrosclerosis), the vascular kidney occurring in essential hypertension without renal insufficiency. Present in 100 per cent of Fishberg's¹ 72 cases, and 90 per cent of Bell-Clawson's² 420 cases.

2. Arteriolosclerotic contracted kidney (benign decompensated nephrosclerosis—Fahr, genuine schrumpfniere), the histologic picture is merely that of a far-advanced stage of group 1.

3. Malignant nephrosclerosis (Fahr).

It is obvious that there are various grades of vascular kidney between the noncontracted group 1, and the contracted group 2, dependent upon when the hypertensive vascular renal lesion is abruptly terminated in its cycle by an extrarenal vascular accident. We are concerned with groups 2 and 3. Pathologically, they are easily separated, but clinically, it is very difficult at times to distinguish them. In the former the kidney is small, contracted, arteriolosclerosis of vasa afferentia is present, combined with arteriosclerosis of the arcuate and interlobular arteries, which causes the obliteration of renal parenchyma with its resultant contraction. These vascular alterations may destroy a sufficient number of glomeruli to produce uremia. But as a rule, this type of termination is rare because the sclerosis is a slow process and the patient with essential hypertension is in constant danger of a cerebral or coronary vascular accident, which terminates the picture long before the replacement of a majority of glomeruli by fibrous tissue. Then again, cardiac decompensation due to high blood pressure plus vascular alterations in the myocardium will convert a partial renal insufficiency to a complete one by aggravating the renal circulatory embarrassment.

Malignant nephrosclerosis may superimpose itself, as it often does, on a partial renal insufficiency due to arteriolosclerosis and so interrupt the sclerotic process in its further progress.

It is evident that of the 10 per cent of essential hypertension who die in uremia a small percentage of these succumb to the arteriolosclerotic contracted kidney. Bell and Clawson, who reported 420 cases of primary arterial hypertension including 36 cases of death of uremia, pointed out that when uremia had

notice, especially when it is known the nephritic edema usually occurs, if it does, about the tenth day after the onset of sore throat, at which time the patient is usually out of bed and attending to business. Too often do we encounter rheumatic cardiacs who never experienced an attack of acute arthritis, "growing pains," and deny other rheumatic manifestations.

When a case has been followed for a long time from period of hypertension without renal insufficiency to the development of renal insufficiency, a diagnosis of nephrosclerosis can be made, benign, decompensated (Fahr) or malignant, depending on the clinical picture, but chronic glomerulonephritis can be definitely excluded.

Questioning our patient for symptoms of past attacks of acute nephritis developed nothing. Our patient is fifty-six; her past history except for frequent colds is negative, she felt perfectly well until three years ago when she suffered with headaches and the examining physician she consulted told her the blood pressure was 270. She felt well, except for headaches and infrequent slight attacks of dizziness, until three weeks before entering the hospital, when her symptoms became markedly aggravated. Signs of renal insufficiency appeared, vomiting, terrific headaches, drowsiness. Her nonprotein nitrogen on admission was 85, creatinine 3.6 mg. per 100 cc.

This history, at times, characterizes the malignant nephrosclerotic. There is an antecedent history of hypertension which varies in some cases from six months to ten years, often symptomless, at times accompanied with its attendant symptoms of headache, weakness, nervousness, *to a more or less degree*, then the tragic story that the headaches are uncontrollable, vision is failing, vomiting and obstinate nausea distress, marking the clinically passing into the malignant nephrosclerotic state. When malignant nephrosclerosis occurs in the young adult (twenty to thirty), the course is very severe and they go rapidly into kidney failure; at times they drop so quickly into uremic coma that little previous history can be obtained of any consequence. The factor of age is, at times, helpful. When the patient is around twenty, the observed kidney picture is most probably

in renal cortex. About 10 per cent of the glomeruli are involved in this acute arteriolosclerosis. According to Klemperer, "one is surprised to find an apparent incongruity between severe functional damage and the state of preservation of the renal parenchyma."

Involvement of choroid was seen in every case examined by Klemperer and Otani. These choroid changes revealed cellular intimal proliferation, severe arteriohyalinization in all the cases and actual arteriolonecrosis in one instance. These profound alterations are of inestimable value in the interpretation and understanding of the typical fundus in this disease. In the other organs, with the exception of pancreas and spleen, arteriolosclerosis was less constantly found. It must be remembered that involvement of the small and smallest arteries was never general. It is generally agreed that there is no essential qualitative difference between the condition of the kidney in benign and malignant nephrosclerosis. The difference appears to be one of degree rather than of kind. The pathologic picture in the latter is an expression of a severe grade of arteriolosclerosis in which the ischemia due to arteriolar spasm plays an important rôle. Often, after microscopical study the pathologist is puzzled in the differentiation between malignant nephrosclerotic kidney and the secondary contracted kidney. Klemperer and Otani after examining 37 cases had difficulty in establishing and relegating 2 such cases to their proper category. The clinician should tread carefully into such diagnostic realms, not unmindful of the many pitfalls that beset him. With this in mind, let us now carefully analyze our case, and enumerate and evaluate the clinical facts that point to malignant nephrosclerosis.

The history is of paramount importance in the differential diagnosis. When one obtains a history of an acute nephritis following acute tonsillitis, scarlatina, or when recurrent attacks of acute nephritis are observed, the diagnosis of secondary contracted kidney can be safely made. Every clinician is familiar with the occasional unreliability and fallibility of past history; the patient might have had a slight puffiness of the face following the attack of sore throat that was so slight that it escaped

in 12 cases. One may rightfully assume that had the cerebral accident been postponed for a time in the last case, renal arteriolar necrosis might have progressed far enough to produce renal insufficiency. Renal failure was a more conspicuous observation in their series; this difference may be ascribed to the fact that more of their cases were seen in a terminal state. The contention that the group of malignant hypertension is closely allied to malignant nephrosclerosis group is certainly well founded, and future work will corroborate and substantiate the viewpoint that they are identical.

In reference to the blood count, usually, when renal insufficiency sets in with azotemia there results a secondary anemia, which usually parallels the retention; as the retention mounts the anemia increases. This is utilized by many as a prognostic index. The anemia is not pronounced in the malignant nephrosclerotic as compared with the chronic glomerulonephritic, due to the fact that the kidney failure strikes suddenly and severely; the nitrogenous retention does not last long as the entire clinical is short, whereas the chronic glomerulonephritics can and do carry the azotemia over a longer period of time. Our case showed a moderate secondary anemia, 2,500,000 to 3,000,000 red cells. Ten red cell counts were tabulated for the 7 cases reported by Murphy and Grill. Five counts were over 4,000,000 (one being 5,000,000); three were over 3,000,000. The optic disk is usually paler in the secondary contracted kidney. Unlike the anemia and blood pressure, the eye signs are most helpful and indispensable in the diagnosis of malignant nephrosclerosis. They are briefly—edema of disk with its indistinct margins, edema of retina and hemorrhages, cotton-wool exudates, stellate figure in macula. The distinguishing factor is the papilledema; this differentiates the hypertensive neuroretinopathy (Fishberg) from the lesions observed in retinal arteriosclerosis present in essential hypertension. All cases of malignant nephrosclerosis reported thus far present this characteristic fundus picture. It can also occur, lest we forget, without renal lesions—adenoma of supra-renal cortex, acute lead poisoning. When a patient with essential hypertension develops hypertensive neuroretinopathy

that of chronic glomerulonephritis on the basis of percentage statistics. It must be remembered that Klemperer and Otani reported a case of malignant nephrosclerosis in a boy of eight and a half years; the youngest in Shapiro's series was twenty-four; though the average age computed for all the groups is forty.

The blood pressure readings may give a helpful clue, but are in no sense diagnostic. The systolic and diastolic pressures are, as a rule, higher in malignant nephrosclerosis than in chronic glomerulonephritis. Systolic pressures of 250, diastolic over 150 are not uncommon in the malignant state. Our patient's systolic varied from 270 to 220, diastolic 150 to 130. It persisted very high with little or no remissions. Apropos of question of blood pressure, comment on the clinical entity of "malignant hypertension" is pertinent to our discussion. The term "malignant hypertension" was first used by Vollhard and Fahr to designate cases of renal arteriosclerosis in which renal failure later developed. They later introduced the anatomical expression "malignant nephrosclerosis" to designate changes in kidney characterized by necrosis of afferent glomerular arterioles. Keith,⁵ Wagner, and Kernohan⁵ used malignant hypertension to characterize a group of patients with severe hypertension and neuroretinitis, observing the fact that this syndrome may be superimposed on a previous general arteriosclerosis or on an essential hypertension. These patients are considered by many as malignant nephrosclerotics or malignant nephrosclerotics prior to intervention of renal insufficiency. When the necrotizing lesions in the cortical arterioles manifest themselves clinically with its attendant uremic symptoms they are classed by all as malignant nephrosclerotics. A number of Keith et al. series died of uremia, but more of the series succumbed to a cerebral or coronary vascular accident before the devastating kidney picture could appear. It should be mentioned, only four autopsies were obtained in the series of 81 cases. In 16 cases of malignant hypertension reported by Murphy and Grill,⁶ six died of uremia, one died of apoplexy; all seven showed the characteristic histologic picture of malignant nephrosclerosis. Autopsies were obtained

tion, obliterating endarteritis, arteriolonecrosis of vasa afferentia, convey, and rightfully so, a serious picture of a vascular altered kidney. Yet, it is surprising how often the microscopical examination of the urinary sediment reveals few or no red blood cells. Klemperer and Otani state, "the specific gravity of the urine was always low, albumen was present regularly, the sediment contained hyaline and granular casts, white blood cells, and occasionally blood." Murphy and Grill for their 7 cases tabulated fourteen urine examinations. Microscopical examination of urinary sediment was negative six times, four showed few red cells, four showed many red cells. Thirty-one urine examinations of our patient showed, only on four occasions, red blood cells from three to ten per field. But, in some cases frank hematuria is a prominent symptom.

The luetic history in our patient raises the question whether syphilis is an etiologic factor in the causation of malignant nephrosclerosis. Fahr expressed the belief that the vascular poisons of syphilis, lead and the virus of rheumatic fever affect the renal arterioles and are responsible for the accelerated athosclerotic type of malignant nephrosclerosis. In his opinion, syphilis is an important factor in its pathogenesis. In the series of Klemperer and Otani, one had a positive Wassermann, but there was no syphilitic organic lesion present. In the series of Shapiro, 23 cases, eight were syphilitic; and he concludes that syphilis predisposes to nephrosclerosis but no more to the malignant than the benign (essential hypertension).

Autopsy was performed by Dr. A. Plaut and a brief synopsis of the protocol is given. The left kidney weighed 60 Gm., right kidney weighed 105 Gm. Several small hemorrhages in both kidneys. Surface irregularly finely granular. Markings of kidney obliterated with irregular gray areas on section. Pelvic fat increased. Pelvic hemorrhages present. Microscopical examination shows obliterative endarteritis plus arteriolonecrosis. *Diagnosis:* Malignant nephrosclerosis. Syphilitic aortitis present. Heart weight, 485 Gm. and showed a mild fibrinous pericarditis.

(neuroretinitis), he can be considered entering the malignant nephrosclerotic state. Can this fundus picture occur in chronic glomerulonephritis? According to statistics compiled by Fishberg, 17 of 55 cases of secondary contracted kidney exhibited hypertensive neuroretinopathy. Keith et al. maintain they can differentiate the ophthalmoscopic picture of hypertensive neuroretinopathy in the malignant hypertension (malignant nephrosclerotic) from that occurring in chronic glomerulonephritis. Our patient showed edema of right disk plus bilateral retinal edema which subsequently cleared up.

It is interesting to note that during the last ten days of her life, and probably longer, the edema of the right disk and the edema of both retinas had completely cleared up, despite her uncompromising clinical status that pursued its relentless course. Many who had examined the patient then for the first time opposed the diagnosis of malignant nephrosclerosis, disregarding the severe and rapidly progressing clinical picture. Absence of the typical eye signs definitely and unequivocally eliminated, they contended, malignant nephrosclerosis from further consideration. All observers in their reports have stressed the importance of the indispensable signs of neuroretinitis (hypertensive neuroretinopathy) in the diagnosis of malignant nephrosclerosis. The presence of a unilateral edematous disk is very uncommon, though it can occur according to Moore.⁷ The disappearance of papilledema in malignant nephrosclerosis is unknown, unlike chronic glomerulonephritis where the papilledema may improve greatly, or in rare instances, disappear entirely. Dr. Slomka, in retrospect, believes that the edema of the disk might have been intimately associated with the edema of the surrounding and overlying retina, and probably was not papilledema. The dictum—no neuroretinitis, no malignant nephrosclerosis—requires modification.

Before leaving this important sign of hypertensive neuroretinopathy, it should be emphasized, though it is conceded to be an ominous prognostic sign that forebodes impending evil, one should not attempt, from this alone, to calculate and predict the future span of the victim's life. The histologic descrip-

and puffiness of the eyelids, coming on during the night and subsiding by day, has been noticed. In spite of this edema, the patient has lost 30 pounds in the past three years. A year ago severe itching developed over the chest and abdomen lasting a month and leaving brown patches on the skin after it subsided. During the six months prior to admission she noticed a progressive weakness, loss of appetite, nausea, and occasional bleeding from the nose. Her headaches were becoming more severe than ever. On admission, it is weakness that is the outstanding complaint.

The patient, as you see, is an ambulatory, middle-aged woman, appearing chronically ill. She has the "nephritic facies," a waxy pallor and puffiness of the eyelids. There is an ammoniacal odor to the breath, but she is not drowsy, indeed, she is mentally alert. Her tongue is coated brown; the tonsils and anterior faucial pillars are injected. There are no ulcerations of the mucous membranes. The lungs are clear. The heart is enlarged to the left, with a strong and diffuse apical impulse in the sixth interspace, $9\frac{1}{2}$ cm. to the left of the midline. The first sound is of good quality at the apex; the aortic second sound is much louder than the pulmonic second, and is of a ringing quality. There is a soft systolic blow heard at the apex and transmitted into the axilla. The rate is 80. The blood pressure has fluctuated between 216/134 on admission and 140/100. Abdominally neither the kidneys nor any other masses are felt. There is however a definite bilateral costovertebral tenderness, more marked on the right side. The extremities are slightly edematous. The skin, besides being sallow, shows brown pigmentation over the chest and abdomen, over the same areas that she had severe itching one year ago. Except for a marked hyperreflexia of all four extremities, the neurological examination is negative. The temperature has been normal since admission. At no time did this patient have any gross hematuria, twitching, convulsions, vomiting, diarrhea or any visual disturbances.

Whereas the general appearance, physical examination, in conjunction with her history make us suspect immediately a renal lesion, it is the laboratory findings which indicate the exact extent of kidney involvement. Since admission the most constant findings were in the urine. It always maintained a low

Case III.—Mrs. S. L. is a married woman of forty-seven, born in Russia, admitted to this hospital on September 30, 1932, complaining of weakness, loss of appetite, nausea, and occasional nose bleeds for the past six months. Her family history is entirely irrelevant. Her past history is especially interesting in that she had scarlet fever at the age of eighteen, apparently uncomplicated at that time. She has had chest colds and sore throats as far back as she can remember. Twelve years ago she was delivered uneventfully of her first child. But when she became pregnant again, two years later, her family physician advised termination of pregnancy because of "kidney trouble." In the interval between these two pregnancies, about eleven years ago, she had a very bad sore throat which forced her to bed for two weeks, though no



Fig. 51.

special medical care was called for. She went through the second pregnancy, and again a third six years ago, each time against her physician's warning that the existing kidney disease would make the delivery hazardous.

Ten years ago, during the first pregnancy, she noticed for the first time severe frontal headache and pallor of the face which have persisted to date. Eight years ago she first noticed shortness of breath, palpitation, precordial discomfort and pain over both kidneys, all appearing on moderate physical exertion and subsiding with rest. She was unaware of any hypertension, however, until she was refused insurance six years ago because of both "kidney trouble and high blood pressure." For the past five years there has been some polyuria and nocturia (D/N: $\frac{2}{1}$). During the past year edema of the legs

fever at eighteen and the severe tonsillitis that the patient recalls so well after the first pregnancy. The fact that the patient had a free interval of about twenty years of apparent good health does not rule out the first possibility. Such cases of chronic glomerular nephritis have repeatedly been encountered. But since we do know that the urine during the first pregnancy was normal, and that it was obviously abnormal a few months after the tonsillitis, we have more cause to consider the tonsillitis to be the etiologic factor in her illness. Even in the absence of a toxic etiologic factor such as we have here, this case would be considered typical of chronic glomerular nephritis because the picture of severe kidney involvement, as corroborated by the urinary findings, developed many years before hypertension manifested itself. It is to be noted that the eyegrounds show the degenerative changes of retinal arteriosclerosis and not the hypertensive neuroretinopathy seen in malignant nephrosclerosis. The eventual outcome in this case is that of renal failure with uremia which will terminate the picture in some future acute recurrent attack.

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specific gravity varying between 1.010 and 1.005. In the dilution test, the specific gravity of specimens collected every hour after the oral administration of 1500 cc. of water was (1) 1.010, (2) 1.008, (3) 1.005, (4) 1.006, (5) 1.006, (6) 1.006, (7) 1.008, (8) 1.006. Albumin was always 3+. Esbach test, 4 Gm. albumin in twenty-four hours. The centrifuged specimen showed at first only occasional granular, epithelial, and hyaline casts, with 2 to 3 red blood cells per high power field and many white blood cells. After her first week in the hospital there were no more casts or red blood cells but the white blood cells persisted. The blood chemistry on admission showed only a moderate nitrogen retention: glucose 95, urea nitrogen 47, nonprotein nitrogen 75, creatinine 5, uric acid 6.6, chlorides 600, cholesterol 222, calcium 9.8, phosphorus 6, total proteins 5.2; albumin-globulin ratio 1.3; indican 1.7, icteric index 14. Since then the nonprotein nitrogen fluctuated between 85 and 60, the creatinine remaining the same, 5 mg., even when the nonprotein nitrogen was 60. The blood count showed a moderately severe anemia with red blood cells of only 2,500,000 and hemoglobin of 38 Sahli units. This improved only slightly for awhile, and is now again at the admission level. The white blood count and differential smear are within normal limits. Sedimentation rate was 67 mm. on admission but fell to 40 mm. at the present time (eight weeks after admission). Serology is negative. The basal metabolic rate is 8+. As you recall, she had no visual disturbances till time of admission, when she began to complain of impaired eyesight, especially on the right. Both fundi on admission showed pale disks and markedly sclerotic vessels. Some thrombosed vessels were seen in the right fundus, as well as partial stellate exudate formation in the macular region. There have been no changes in the fundi during her stay here.

The problem in this case is much simpler than that presented by the two previous ones. The chronicity of the disease, the sallow and anemic appearance of the patient, the chronic hypertension plus the urinary and blood evidence of impaired renal function point to chronic glomerular nephritis. As for the etiology, we have the choice of two possibilities—the scarlet

fever at eighteen and the severe tonsillitis that the patient recalls so well after the first pregnancy. The fact that the patient had a free interval of about twenty years of apparent good health does not rule out the first possibility. Such cases of chronic glomerular nephritis have repeatedly been encountered. But since we do know that the urine during the first pregnancy was normal, and that it was obviously abnormal a few months after the tonsillitis, we have more cause to consider the tonsillitis to be the etiologic factor in her illness. Even in the absence of a toxic etiologic factor such as we have here, this case would be considered typical of chronic glomerular nephritis because the picture of severe kidney involvement, as corroborated by the urinary findings, developed many years before hypertension manifested itself. It is to be noted that the eyegrounds show the degenerative changes of retinal arteriosclerosis and not the hypertensive neuroretinopathy seen in malignant nephrosclerosis. The eventual outcome in this case is that of renal failure with uremia which will terminate the picture in some future acute recurrent attack.

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CLINIC OF DR. A. ALLEN GOLDBLOOM

BETH ISRAEL HOSPITAL

DIAGNOSTIC IMPORTANCE OF BLOOD VOLUME AND CARDIAC OUTPUT STUDIES IN A BORDERLINE CASE OF THYROTOXICOSIS

THE typical case of thyrotoxicosis seldom offers difficulty in diagnosis; as a rule, the diagnosis is so readily made as to make basal metabolic studies superfluous. On the other hand, many functional affections such as neurocirculatory asthenia or the Basedowoid cases of von Bergmann, as well as such organic affections as incipient tuberculosis particularly in asthenic individuals with instability of the vasomotor system offer extreme difficulty in their differential diagnosis. In many such cases, the basal metabolic figures range as high as $+40$ to $+50$ or more, without the presence of thyrotoxicosis. As a result of this Lahey¹ pointed out recently that the value of basal metabolic studies is tending to depreciate in borderline cases.

The employment of any laboratory method, even a complicated one, that will yield diagnostic data in the borderline case is highly important. If a diagnosis of some nonexistent disease is made the damage may be irreparable, especially in a psychoneurotic or an impressionable individual. If incipient disease is overlooked in the borderline case and the patient is not cautioned, the possibility of a cure during the most favorable period of the life history of the disease may be precluded.

The case presented illustrates the usefulness of blood volume and cardiac output methods in arriving at a diagnosis. Before presenting the case to you, we wish to take this opportunity to express our appreciation of the collecting of the bloods by Dr. Isaiah Libin and of the technical assistance rendered by Mr. Paul K. Roht.

method of determining the arteriovenous oxygen difference and from this estimated the cardiac output. After our patients—already in a basal state—had rested ten minutes to accommodate themselves, the basal determinations were made in both the sitting and lying posture. The gas mixture was made up of 0.7 liter of acetylene, 0.3 liter of oxygen, and up to 3 liters of air, making a concentration of 20 to 23 per cent of acetylene. We followed the method advocated by Bansi and Groscurth,⁸ using their small samplers and valve. The patient was allowed to breathe through a mouthpiece and corrugated tubing into Douglas sacks which collected the expired air. The side arm of these sacks permitted a sample to be taken for the determination of carbon dioxide and oxygen, while the sack was being emptied and the contents passed through a meter that registered the amounts. By this means we were able to determine the oxygen consumption and carbon dioxide elimination in a definite time and could thereby calculate the respiratory quotient. This oxygen consumption per minute was utilized in the determination of cardiac output as follows:

$$\text{Arteriovenous oxygen difference} = \frac{\text{Oxygen difference} \times \text{middle alveolar expansion} \times 0.00974 \times (\text{Ba} - 48.1)}{\text{Acetylene difference}}$$

$$\text{Minute volume} = \frac{\text{Oxygen per minute (Douglas Sacks)}}{\text{Arteriovenous oxygen difference}}$$

Note.—Ba = Barometric pressure reading.

48.1 = Water vapor tension.

All our calculations were reduced to standard conditions of zero degrees and 760 mm. mercury barometric pressure.

TERMINOLOGY

The heart normally pumps out a certain amount of blood per unit time from the ventricle into the periphery. This is known as the *cardiac output*, *minute volume*, or *circulatory minute volume*, and is expressed in terms of liters per minute. The amount of blood ejected by the left ventricle with each systole is referred

in the Van Slyke apparatus. The dissociation curves and p_{H} of the blood were determined. From the minute volume determinations, as advocated by Grollman,⁷ we were able to obtain our data of oxygen consumption, arteriovenous oxygen difference, respiratory quotient, and the metabolism of the body.

Blood Volume Determinations.—Upon collection of the bloods, the analysis was determined as soon as possible. To each amount of blood collected, there was added 10 per cent solution of an anticoagulant solution of the following: ammonium oxalate 2; sodium chloride 0.8; aqua dist. up to 100. The bloods were thoroughly shaken in a special collecting tube. From the blood not containing the dye, 1 cc. was withdrawn and later utilized for the hematocrit determinations. The remainder of the blood as well as the two samples containing the dye were placed in centrifuge tubes and centrifuged from thirty to forty-five minutes at a speed of 3500 revolutions per minute. This allowed a separation of the blood into packed cells and a layer of plasma. The plasma levels were separated into different test tubes. Ten cc. of the plasma of the first two tubes, not containing the dye, were used to make up a freshly prepared standard as follows: 0.03 Gm. of the trypan red dye was very accurately weighed in special weight glasses on an analytical balance. It is emphatic that this dye be very carefully and exactly weighed out. To this were added 10 cc. of plasma from the first two tubes, thoroughly stirred, and used as a standard mixture for the specific patient. The plasma of the three- and six-minute values were compared to this standard, under a Dubosque colorimeter. Five readings were obtained by two observers from each specimen, the average thereof being utilized. The 1 cc. of blood which was separated from the nondye blood was sucked up into special tubes, carefully scaled into 100 divisions. These were placed and centrifuged at a rate of 10,000 revolutions per minute. The tubes were read directly at the end of thirty minutes. The readings gave the percentage of packed red blood cells in the plasma, or hematocrit.

Cardiac Output Determination.—In order to estimate the cardiac activity of our patients, we used the Grollman acetylene

The amount of blood present in the organism is known as the *total blood volume*, and this may be differentiated into two types. That part of the blood passing the heart once in the circulation is known as the *circulating, active or rapid blood volume*, while that moving more slowly or passively, as through the liver, spleen, splanchnic areas or subpapillary plexus is known as the *stagnant or passive blood volume*. Clinically, when the term "blood volume" is used it refers to the circulating or active type. The dye trypan red is used for the determination of the plasma volume according to the method of Seyderhelm and Lampe.² The total blood volume is computed by utilizing the hematocrit values after rapid centrifuging at a speed of 10,000 revolutions per minute. A freshly prepared 3 per cent sodium cyanide solution is used intravenously for the determination of the arm to arm *circulatory time* (Robb and Weiss method, described by Ellis⁵). This is the shortest time that it takes a particle of blood or a foreign body to traverse the circulatory system from the peripheral veins through the heart and out to the other peripheral arteries. Venous pressure, which is the pressure residue in the vascular system after the resistance in the peripheral vessels (arterioles, capillaries, and venules) is overcome, is determined by a direct method that has recently been demonstrated by Taylor, Thomas, and Schleiter.⁴

CASE REPORT

The patient, Mr. M. G., age twenty-one, was admitted to Beth-Israel Hospital, on the service of Dr. Marcus A. Rothschild, October 24, 1932. He was discharged three weeks later, that is, on November 15, 1932.

The patient's chief complaint was of a productive cough with blood-tinged sputum, following a cold six weeks earlier. During this period of six weeks the patient perspired freely and believed he had run a temperature. The patient related that during the past two years he had experienced many attacks of weakness, dizziness, and loss of consciousness. There was no foaming, biting of the tongue, or involuntary urination during these attacks. The past medical history revealed pneumonia at the age of thirteen, herniotomy at the age of twenty, and tonsillectomy during the past summer.

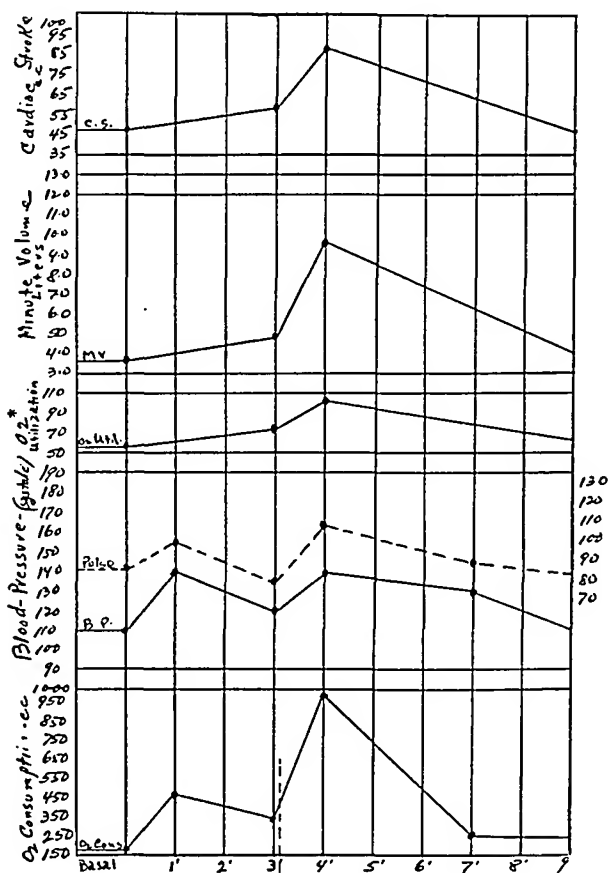
Examination revealed a slightly underweight, relatively pale male. No definite pathology was found except comparative dulness of the right apex, with showers of moist râles that disappeared after coughing. The blood pressure was 108/76. The skin was somewhat cold, moist and clammy with

to as the cardiac stroke, systolic output, or stroke volume, and is the result of the cardiac output divided by the cardiac rate. A number of methods have been advocated for the determination of the cardiac output. The two chief methods in man consist essentially in determining the carbon dioxide or oxygen tension of the arterial and mixed venous bloods and applying the Fick⁹ principle; the second method is to measure the rate of absorption of a foreign gas. The Fick principle is that a knowledge of either the oxygen or carbon dioxide content of the blood before and after passage through the lungs, together with a knowledge of the total oxygen or carbon dioxide exchange, will give the necessary data for calculating the cardiac output. The second method of determining cardiac output is based on measurements of the rate of absorption by the blood of a foreign gas. This has largely replaced all other methods of determining cardiac output because of its simplicity and the consistency of its results. This method is based on the principle that the amount of foreign gas absorbed by the blood in its passage through the lungs is determined by the pulmonary blood flow. Hence, if one determines the rate of absorption of such a gas and knows its solubility in the blood, one can calculate the amount of blood passing through the lungs in unit time. This is the cardiac output. The acetylene gas method (Grollman and Marshall⁷), which has recently come into extensive use, is the method we have employed.

The amount of oxygen given up by a unit volume of blood to the tissues is known as the *arteriovenous oxygen difference* and is expressed as cubic centimeters of oxygen per liter of blood. This gives one a measure of the relative activities of the circulatory and metabolic functions. The arteriovenous oxygen difference divided by the total oxygen content of the arterial blood gives us the *oxygen utilization*, expressed in terms of percentage.

Since the cardiac output of normal individuals would differ considerably because of variations in body size, Grollman⁷ uses the term "cardiac index," which is found to be more constant than cardiac output. Cardiac index is the cardiac output in liters per square meter of body surface.

Figures 52 to 54 show, respectively, values in rest and after exercise in a normal individual (Mr. H. W.), values in rest and



0-1 minute—exercising.

1-3 minutes—resting.

3-4 minutes—exercising.

4-9 minutes—resting.

(● = periods when samples collected.)

* NOTE: Should read: Arteriovenous oxygen difference.

Fig. 52.—Values in rest and after exercise in a normal individual—(H. W.).

after exercise in a neurocirculatory asthenia patient (Mr. M. G., under discussion), and the values in rest and after exercise in a hyperthyroid patient (Mr. H. S.). Figure 55 presents a compos-

a prominence of vasomotor reactions of the skin. There was slight tremor of the hands. Otherwise there was nothing that pointed definitely to a hyperactive thyroid condition.

Laboratory Data.—The blood examination showed hemoglobin, 75 per cent; red blood cells, 4,650,000; white blood cells, 8140; seg., 67 per cent; mononuclears, 33 per cent; polymorphonuclears, 66 per cent; eosinophils, 1 per cent; large lymphocytes, 28 per cent; monocytes, 5 per cent. The sedimentation rate was normal—4 per cent. A Wassermann test was negative. The blood chemistry examination showed glucose 90 mg. per 100 cc. of blood, nonprotein nitrogen, 33, calcium, 9.8. The gastric acidity showed a normal variation of free acidity 36, total acidity 68. The sputum examination was continuously negative for tubercle bacilli. The fecal examinations were also negative.

Various basal metabolism examinations revealed the following:

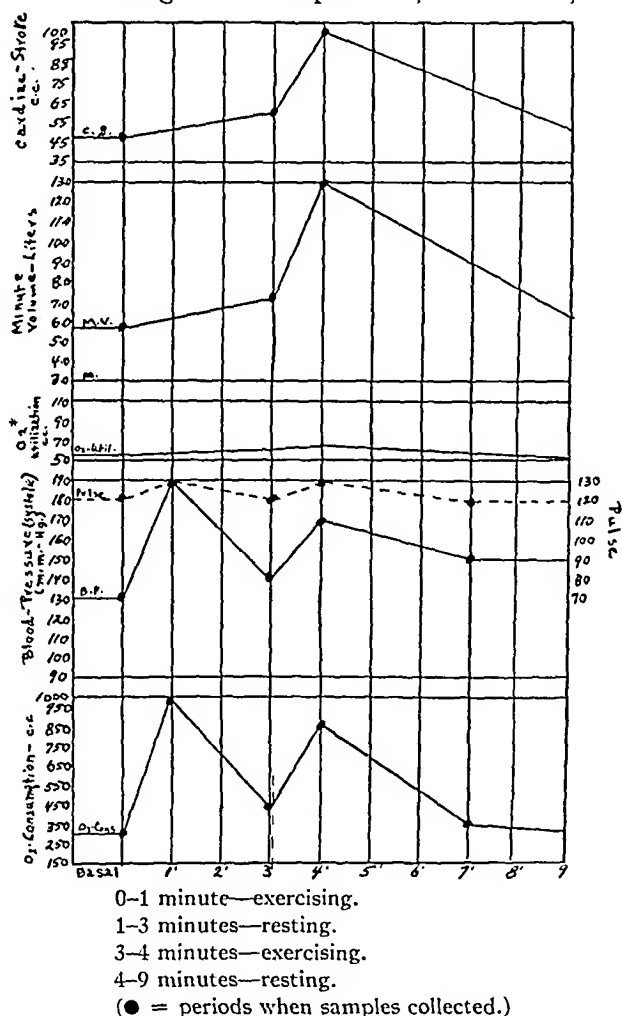
October 28, 1932.....	plus 43
November 2, 1932.....	plus 63
November 4, 1932.....	plus 49
November 7, 1932.....	plus 40
November 9, 1932.....	plus 42
November 14, 1932.....	plus 47*

A note was made that during some of these basal examinations the patient appeared to be nervous and faint. While a basal cardiac output was being determined, the patient went into one of his attacks of "unconsciousness," during which the blood sugar showed only 68 mg. There was twitching of the eyelids with a slight moistness of the skin. The patient was not actually unconscious; he could be aroused and was responsive.

The history in this case and the findings could not lead us to a definite diagnosis. The unusual laboratory data were the increased basal metabolism figures. The constitutional make-up of the individual, including a tendency to perspiring freely, a moist, clammy skin, a tremor of the hands, and an occasional rapidity of the heart rate, indicated an imbalance in the vegetative system. However, since there were evident variations in the basal metabolism rates, a diagnosis of thyrotoxicosis, despite the fact that clinically the patient did not ever impress us as a true case of hyperthyroidism, could not be disregarded. Therefore, all available laboratory procedures, including blood volume and cardiac output studies, were carried out in an effort to clear the diagnosis.

* A basal metabolism test done by Dr. S. Mausner following the patient's discharge from the hospital showed plus 19.

are higher, per kilo of body weight, than found in either the normal patient or Mr. M. G., the patient under discussion. Mr. M. G.'s readings of blood pressure, hematocrit, and blood

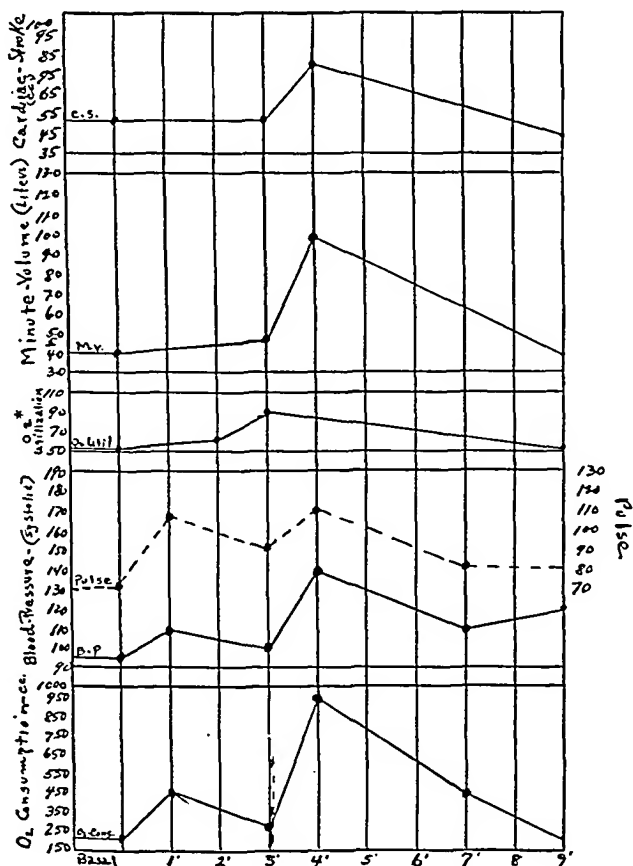


* NOTE: Should read: Arteriovenous oxygen difference.

Fig. 54.—Values in rest and after exercise in a hyperthyroid patient—(H. S.).

volume are on a lower level than normal. The cardiac output and oxygen consumption, both in a basal state and after mild exercise, of the patient under discussion, Mr. M. G., follow those

ite study of the values in rest and after exercise of the patient under consideration and a hyperthyroid patient, Mr. H. S.



0-1 minute—exercising.

1-3 minutes—resting.

3-4 minutes—exercising.

4-9 minutes—resting.

(● = periods when samples collected.)

* NOTE: Should read: Arteriovenous oxygen difference.

Fig. 53.—Values in rest and after exercise in our neurocirculatory asthenia patient—(M. G.).

It will be noted that Mr. H. S., the hyperthyroid individual, shows a higher pulse pressure and a more rapid circulatory time than the normal individual, and that his blood volume readings

The findings after exercise in the normal person and in the individual under discussion were similar, that is to say with an increase of oxygen consumption there is a corresponding increase of minute volume. When our patient is compared with the hyperthyroid individual, however, one notes a variation. In the hyperthyroid individual, there is a greater increase of oxygen consumption with a greater increase of cardiac output and cardiac index. The cardiac stroke of the hyperthyroid patient is diminished, however, due to tachycardia. The tachycardia and the increased blood pressure in the thyroid must produce a high basal cardiac index in association with a diminished cardiac stroke. Upon exercise, our patient does not react like a hyperthyroid individual, the latter having a greater oxygen consumption with a higher minute volume and cardiac stroke. There is also a greater rise in blood pressure and pulse. Another characteristic finding in the hyperthyroid individual, and absent in the patient under discussion, is that the arteriovenous oxygen difference remains on a constant level; it does not increase, or slightly.

A very important point of differentiation and one of even more diagnostic value than the findings of basal studies, is the time required for the cardiac output to return to its normal level after exercise. In a normal individual this is eight minutes. The curve of the patient under consideration follows fairly closely that of the normal individual. In the hyperthyroid patient, however, the time is protracted, exceeding the eight-minute period.

There is no doubt that the studies of blood volume and cardiac output in the patient under discussion indicate readings much more nearly those of a normal individual than corresponding to the hyperthyroid figures. We believe, therefore, that the symptoms of which Mr. H. G. complains are definitely not due to thyrotoxicosis, despite the very high basal metabolic readings, but are an expression of neurocirculatory asthenia. This tends to prove the assertion of Lahey, and others, that variable basal metabolism rates, extending as high even as a +63, should not be concluded to be of thyrotoxic origin. They may be the result of an imbalance in the vegetative system.

of a normal patient. The basal minute volume and cardiac index for Mr. M. G. are slightly above those of a normal patient,

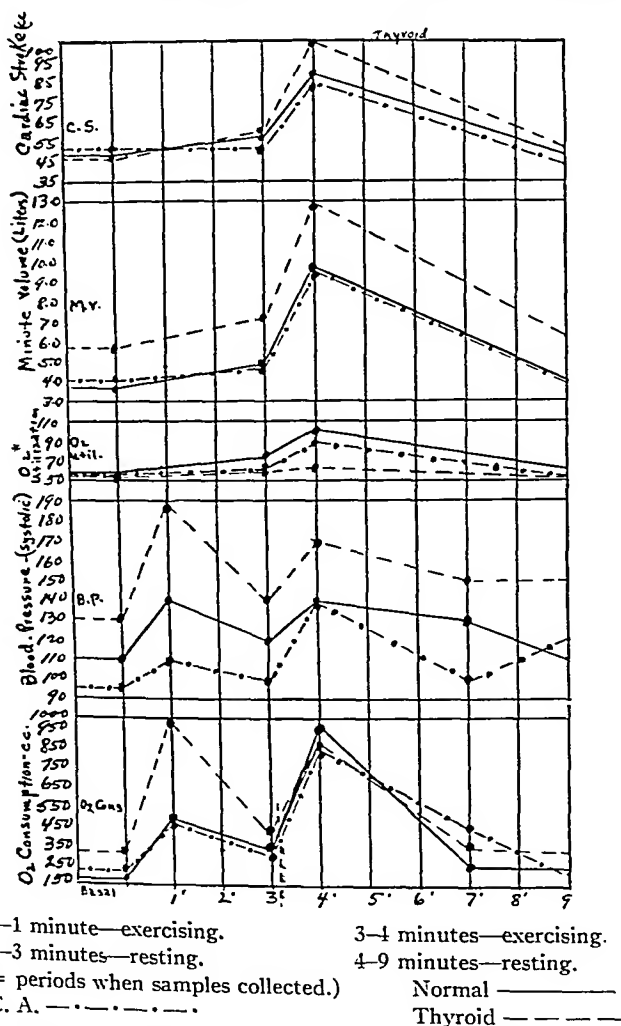


Fig. 55.—Composite values of a normal—a neurocirculatory asthenia and a hyperthyroid patient—in rest and after exercise.

but they are not near those of the hyperthyroid case, who shows a basal minute volume of 5.7 liters and a cardiac index of 3.06 (Fig. 54).

TABLE 2
 PROTOCOL OF VALUES IN OUR NEUROCIRCULATORY ASTHENIA PATIENT (M. G.)

State.	Amount, liters.	Oxygen consump- tion, cc.	Carbon dioxide consump- tion, cc.	Resp. quot.	Pulse.	Blood pressure.	Arterio- venous difference, cc.	Minute volume, liters.	Cardiac stroke, cc.	Cardiac index.	Remarks.
Basal	38.0	229	220	0.955	76	95/60	57	4.01	52	2.53	Sitting on chair.
	Patient	exercising	1 minute								After walking 2 flights of stairs and exercising for one minute.
0-1'	12.0	467	445	0.952	108	110/70	Dyspneic, dizzy.
1-3'19"	17.0	291	235	0.808	92	100/60	63	4.7	51	2.97	Slightly dyspneic.
0-1'21"	20.0	850	855	1.00	112	140/60	90	9.4	84	5.94	Walked 2 flights of stairs—sample of acetylene taken while exercis- ing for one minute.
1-3'	100	110/60	Resting—slightly dizzy.
3-6'	33.0	454	356	0.784	88	100/60	Hyperpneic.
6-8'21"	17.0	214	179	0.835	88	120/70	55	3.9	43	2.46	Hyperpneic, dizzy.

TABLE 1
 PROTOCOL OF VALUES IN A NORMAL PATIENT (H. W.). COMPOSITE EXERCISE

State.	Amount, liters.	Oxygen consumption, cc.	Carbon dioxide consumption, cc.	Resp. quot.	Pulse.	Blood pressure.	Arterio-venous difference, cc.	Minute volume, liters.	Cardiac stroke, cc.	Cardiac index.	Remarks.
Basal	35.0	210	173	0.823	86	110/60	56	3.7	43	1.9	Patient quite comfortable.
	Patient	exercising	1 minute.	After walking 2 flights of stairs and exercising for one minute.
0-1'	14.0	477	457	0.958	100	140/80	Patient sitting quietly.
1-3'18"	22.0	345	326	0.946	80	120/80	73	4.7	58	2.4	Breathing normally, no dyspnea.
0-1'21"	25.0	995	867	0.871	108	140/80	102	9.7	89	5.1	Walked 2 flights of stairs—sample of acetylene taken while exercising one minute, rapidly moving feet.
1-3'	100	130/80	Sitting quietly.
3-6'	32.0	255	263	1.01	90	130/70	Quiet.
6-8'20"	18.0	250	204	0.816	84	110/70	62	4.0	47	2.1	

TABLE 4

AVERAGE VALUES OF TOTAL BLOOD VOLUMES AND CIRCULATORY TIMES IN A NEUROCIRCULATORY ASTHENIA, A NORMAL, AND A HYPERTHYROID PATIENT

Patient.	Weight.	Height.	Body surface.	Pulse.	Blood pressure.		Venous pressure.	Circ. time.	Hem- atocrit. percent.	Plasma volume.				Blood volume.				Cardiac stroke.
					Sys- tolic.	Dias- tolic.				Total.	Per kilo.	Square meter.	Ideal weight.	Total.	Per kilo.	Square meter.	Ideal weight.	
M. G.— N. C. A.	121	5'5	1.58	76	95	60	5	18	42	2813	51.0	1780	46.9	5228	95	3309	87.1	52
H. W.— normal.	154	5'11	1.89	72	110	60	4	18	50	2886	40.3	1514	40	6442	90.7	3403	90.7	43
H. S.— thyroid.	114	5'4	1.53	110	130	65	8	10	49	3109	60.0	2032	51.8	6744	129.0	4408	112.4	47

TABLE 3
PROTOCOL OF VALUES IN A HYPERTHYROID PATIENT (IL S.)

State,	Amount, liters,	Oxygen consump- tion, cc,	Carbon dioxide consump- tion, cc,	Resp. quot,	Pulse,	Blood pressure,	Arterio- venous difference, cc,	Minute volume, liters,	Cardiac stroke, cc,	Cardiac index,	Remarks,
Basal	34.7	315	240	0.763	120	130/65	55	5.7	47	3.06	Sitting quietly.
	Patient	exercising	1 minute.	After walking 1 flight of stairs and exercising for one minute.
0-1'	25.0	1,004	765	0.761	132	190/100	Slightly dyspneic.
1-3'19"	29.0	436	445	1.00	120	140/60	60	7.2	60	4.7	Still slightly dyspneic.
0-1'20"	20.0	862	822	0.953	132	170/100	65	13.2	100	8.6	Walked 2 flights of stair in 2'30". Exercised for one minute.
1-3'	122	150/75	Resting.
3-6'	30.0	355	297	0.836	122	150/70	Slightly dyspneic.
6-8'21"	18.0	324	283	0.874	120	150/70	52	6.2	51	4.05	

We wish to thank Dr. Marcus A. Rothschild for his kindness in allowing us to present this case and the interest he has shown in the preparation of this paper.

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Fig. 56.—Photograph of patient when seen prior to operation, June, 1932 showing the swelling in the suprasternal notch.



Fig. 57.—Photograph of patient when seen prior to operation, June, 1932, showing the swelling in the suprasternal notch.

CLINIC OF DR. LILLIAN WARNSHUIS

THE THIRD (NEW YORK UNIVERSITY) MEDICAL DIVISION, BELLEVUE HOSPITAL, AND THE METABOLISM CLINICS OF THE UNIVERSITY AND BELLEVUE HOSPITAL MEDICAL COLLEGE, NEW YORK UNIVERSITY

HODGKIN'S DISEASE SIMULATING ADENOMA OF THE THYROID GLAND

THERE are very few references in the literature to Hodgkin's disease of the thyroid gland. Simmonds¹ in a review of Hodgkin's disease published in 1926 mentions the scarcity of such reports. In Germany Beitzke² and Ziegler³ have reported cases where small granulomatous nodules have been found in the thyroid gland associated with manifestations of the disease in other parts of the system. Longcope⁴ reports a very rapidly fatal case at the Pennsylvania Hospital where the lower portion of the neck and supraclavicular region were filled with tumors which extended into the muscles and involved the thyroid gland.

In the following case our attention was drawn first, clinically, to a nodular swelling in the region of the isthmus of the thyroid gland and it was only when the pathologic report was received that a diagnosis of Hodgkin's disease was made.

Report of Case.—*First Admission*.—A. J., age fifteen, female, born in Turkey of Turkish parents was admitted to the Third (New York University) Medical Division of Bellevue Hospital, from the Thyroid Clinic on June 30, 1931. Her chief complaints at that time were: Nervousness of two years duration; "crying and laughing fits" of two years duration; a swelling in the anterior region of the neck of two weeks duration, and difficulty in swallowing of two weeks duration. On questioning, the information was elicited that she slept badly and had had night-sweats for two to three months. There was no history of loss of weight, cough or hemoptysis and the appetite was good. Except for a tonsillectomy performed after some mild attacks of tonsillitis the previous history was negative. The family history was also negative.

the tracheal ring. A diagnosis of chondromyxoma was made and the section was removed for biopsy. The pathologic examination was made by Dr. Douglas Symmers and Dr. Irving Graef of the Pathologic Department of Bellevue Hospital. The report of the specimen of thyroid gland was as follows:

Macroscopical Examination.—Specimen consists of two pieces of tissue, one measuring about $2 \times 2\frac{1}{2} \times 1\frac{1}{2}$ cm., the other about $2\frac{1}{2} \times 1\frac{1}{2}$ cm. The tissue

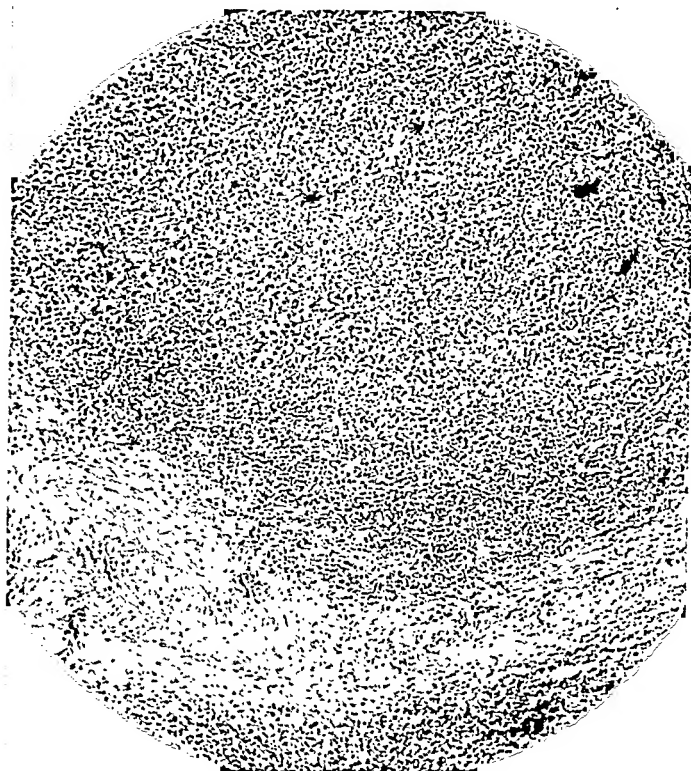


Fig. 58.—Low power microphotograph of a section of the mass. Note the diffuse increase in connective tissue and the absence of normal lymphoid follicles. (Courtesy of the Third Division (New York University) Pathologic Service.)

is very firm, irregular in contour. Tissue cuts with marked resistance. Cut surface is smooth and grayish-white in color. Microscopical examination: Sections from various parts of the tissue revealed a diffuse overgrowth of young connective tissue. Some areas appeared to be delimited by a dense fibrous capsule. Within the capsule no definite lymph node architecture could be seen. However, the young connective tissue framework was infiltrated by innumerable lymphocytes, eosinophils, and a large number of mononuclear

Physical Examination.—The patient was a well-developed girl weighing 114 pounds, pulse rate 110, temperature 98.4 F. Her general appearance was good. There were no outward signs of nervousness and no exophthalmos. There was a swelling about the size of an egg visible and palpable in the supra-sternal notch. This swelling occupied the isthmus of the gland, and appeared to be attached to the lobes. It was firm, unusually hard, of almost cartilaginous consistence. No tenderness was elicited on palpation. There was no pulsation and no bruit was heard. Examination of heart, lungs, and nervous system was negative.

Laboratory Findings.—The urine examination was negative. Blood examination: Red blood cells, 4,200,000; hemoglobin, 70 per cent; white blood cells, 7160; polynuclears, 76 per cent; lymphocytes, 22 per cent; transitionals, 2 per cent. The basal metabolic rate was minus 7 per cent. The x-ray showed no substernal thyroid nor any pathology of the lungs.

A diagnosis of adenoma of the thyroid gland was made and an operation for removal of the swelling was advised, to relieve the dysphagia. It was decided to postpone the operation until the Fall and the patient was discharged on July 11, 1931, promising to return.

Second Admission.—She was readmitted on October 12, 1931, with the previous symptoms of mechanical pressure very definitely increased. To the dysphagia were added a choking sensation, a hacking cough, and periods of dyspnea. She had lost 3 pounds in weight. The swelling had increased in size, and she complained of an increasing nervousness. Sweating was no longer confined to the night, and she was unable to sleep without a sedative. There was neither palpitation nor tremor.

Physical Examination.—The swelling was definitely larger and had apparently grown downward behind the sternum. Otherwise the condition was as described on the first admission. There was no exophthalmos. The chest and heart were normal. The expansion of the chest was good and equal and percussion resonance over it was normal. No adventitious sounds were heard. The pulse rate was 110 and the temperature was 99 F. The basal metabolic rate was minus 4 per cent and minus 15 per cent.

Laboratory Findings.—The urine examination was negative. She had a negative Wassermann examination. The blood chemistry was as follows: Blood sugar, 90 mg., and nonprotein nitrogen, 35 mg.

Blood examination.	10/21/31	10/21/31	10/27/31	11/ 2/31	11/15/31	11/18/31
Red blood cells.....	4,510,000	4,260,000	4,400,000	4,200,000	4,150,000	4,300,000
Hemoglobin.....	88%	86%	85%	80%	83%	80%
White blood cells.....	11,850	10,050	8900	8650	12,800	9800
Polymorphonuclears.....	72%	70%	74%	72%	82%	73%
Mononuclears.....	2%	1%	1%	3%
Lymphocytes.....	25%	24%	26%	28%	13%	24%
Basophils.....	1%	2%

Operation.—The patient was prepared for operation and on October 24, 1931, a partial thyroidectomy was done. The thyroid gland tissue was found to be replaced by an irregular cartilaginous mass which was avascular, of fairly uniform consistency and which had the feeling of gristle.

On cut section there were cartilaginous looking areas mixed with yellowish myxomatous patches, and the posterior surface appeared to form a portion of

which was brassy in quality and productive of thick greenish mucus. There was pain in the chest which tended to be localized to the precordium. The patient was hoarse and had difficulty in swallowing liquids, as they regurgitated. She could swallow solids with greater ease.

Physical Examination.—The patient appeared acutely ill. On the skin over the sternum and tibiae of both legs there was a vesicular eruption which was irritated as a result of scratching. In the left supraclavicular region was a discrete enlarged node, slightly tender. In the left clavicular region was another discrete enlarged gland. Glands were found also in the right and left axillary regions. The inguinal and epitrochlear glands were not palpable.

Laboratory Findings.—The urine examination was negative. Blood examination: Red blood cells, 4,227,000; hemoglobin, 70 per cent; white blood cells, 7750 to 10,800.

The blood pressure examination was 110/78. The x-ray at this time revealed a mass in the superior mediastinum. Radiation therapy and hospital care somewhat improved the general condition of the patient. There was little improvement locally, however, and the cough, dyspnea, and pain in the chest remained. The patient left the hospital on April 6, 1932 and continued the radiation treatments as an out-patient, twice weekly.

Fourth Admission.—She was readmitted May 25, 1932 because of increasing nervousness. On this admission she complained of an increasing sense of substernal pressure and pain. Cough was troublesome, and hoarseness was very marked. The patient looked acutely ill, but she was not markedly dyspneic or orthopneic. There was great difficulty in swallowing.

Physical Examination.—Heart examination showed no enlargement. The rhythm was regular. The pulse rate was 90. There was a blowing systolic murmur at the apex. Subcrepitant râles were heard throughout the lungs. Expiration was prolonged and high pitched. A generalized eruption of excoriated papules and linear excoriations were present. The nodes in the cervical, supraclavicular and axillary regions were increased in size and very hard. The patient was treated with deep x-ray therapy, and showed a slight temporary improvement, but the cough and hoarseness due to recurrent laryngeal nerve pressure increased, and it soon became necessary to feed her by nasal tube.

The patient died on July 5, 1932, thirty-seven days after final admission. Permission for autopsy was not obtained.

Discussion.—The rarity of Hodgkin's disease of the thyroid gland is obvious from the scarcity of such reports in the literature. In this case the disease, although not affecting the thyroid gland itself, simulated a nontoxic adenoma of the thyroid, clinically. There was a hard, painless nodular swelling situated in the suprasternal notch producing mechanical irritation, in a young girl whose general health was good at the time she was first observed. There were at this time no symptoms that

giant cells. There were occasional multinucleated giant cells. In the fibrous capsule extension of the lymphocytes and eosinophils was noted in the inner layers. No thyroid epithelium was seen. Diagnosis: Hodgkin's disease.

Convalescence was uneventful and the patient was discharged on November 23, 1931. x-Ray therapy was begun in the hospital after the diagnosis had been reported. This therapy was continued. On December 7th the patient returned to the clinic for examination. At this time a small nodule

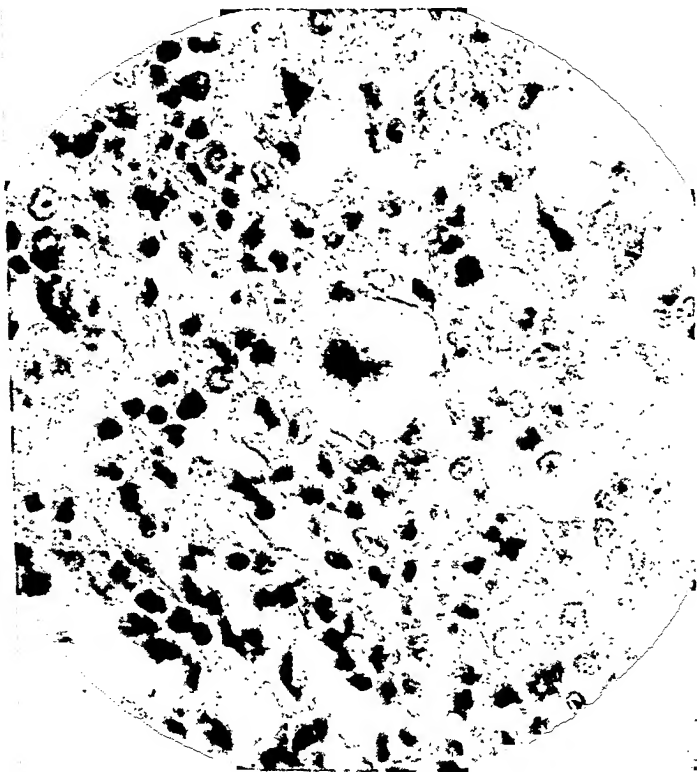
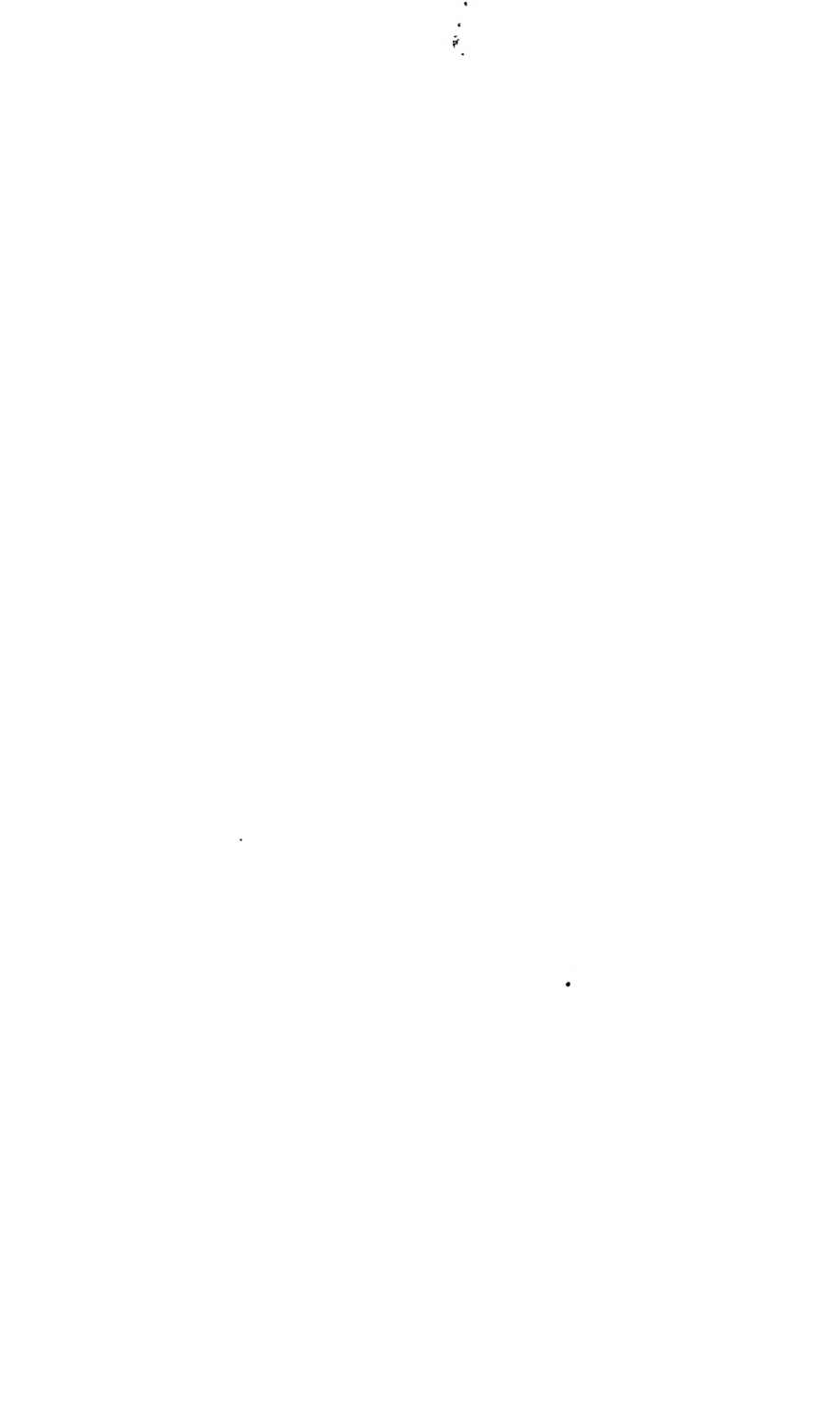


Fig. 59.—High power microphotograph to show various cell types, including a multinucleated giant cell in the center of the field. (Courtesy of the Third Division (New York University) Pathologic Service.)

was seen and felt on the left side of the neck. On her next visit to the clinic, December 21st, two weeks later, a hard painless nodule about the size of a walnut was found above the left clavicle. In February, 1932, small nodules were palpable in both axillae. Her general health at this time was poor. She was extremely nervous and anxious. Insomnia was one of her most obstinate symptoms.

Third Admission.—The patient was readmitted to the hospital on March 26, 1932. At this time the patient complained of a constant hacking cough



would have suggested such a complication as Hodgkin's disease. The basal metabolic rate was within normal limits and the laboratory findings were negative.

The subsequent course of the disease, however, was quite different from that of a benign adenoma. In the three and a half months following her first admission to the hospital, symptoms developed which substantiated the pathologic diagnosis and which showed conclusively that the tumor was not a nontoxic adenoma. The growth of the tumor was so rapid that mechanical interference with swallowing and breathing dominated the picture. Prior to operation the x-ray report was negative for any substernal mass. On the third admission there was evidence of a mass in the mediastinum.

Deep x-ray therapy was of no avail in arresting the progress of the disease. The rapidly fatal course was probably partly due to the location of the main mass of the tumor.

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In both of these groups the successful treatment of the condition depends on increasing the intake of food. This means that the appetite has to be stimulated. In the man who has always been underweight this is a matter of mental effort. In the individual who has lost weight the distaste for food must be overcome. Sometimes the person can do this by forcing himself to eat. The individual may require a week or so to accommodate himself to the increased bulk. In these cases a gastric sedative may help overcome the feeling of distress that at first follows the taking of the larger amounts of food. We have not used any stomachic in the cases presented. Once the individual has managed to eat the whole diet the stomach apparently becomes used to the increased bulk and then the appetite returns. Recently insulin has been used in malnutrition. Nahum and Himwich¹ report 4 cases treated with insulin. The greatest gain was 22.5 pounds in twenty-eight days and the least 15 pounds in thirty-nine days. Forty-five to 65 units of insulin were given daily. The effect of insulin is attributed to the fact that it improved the appetite enormously, so that the amounts of food taken after treatment were greatly increased. These observers advance the suggestion that the capacity of the stomach is increased after insulin injections. This is substantiated by the work of Bulatoa and Carlson² who injected insulin in normal fasting dogs and obtained an increase in gastric motility. This was accompanied by hypoglycemia. Appel³ and his associates report 17 psychopathic cases treated with insulin. On diet alone the average gain of weight was 9/10 pound weekly. With insulin the gain was 2.4 pounds weekly. The authors however admit that the patients did not eat all of the diet prior to the administration of insulin. In all of the work reported up to this time with insulin the action seems to be on the appetite. We feel that if the patient can take the required amount of food the gain of weight will be as great without insulin as with it. The advantage is that the patient does not have the bother of taking insulin or the danger of hypoglycemia. It is also possible for the patient to treat his condition without being hospitalized, which the administration of large doses of insulin should require.

CLINIC OF DRS. ELAINE P. RALLI AND MARSHALL S. BROWN, JR.

FROM THE METABOLISM CLINICS OF THE UNIVERSITY AND BELLE-
VUE HOSPITAL MEDICAL COLLEGE, NEW YORK UNIVERSITY
AND THE THIRD (NEW YORK UNIVERSITY) MEDICAL DIVISION,
BELLEVUE HOSPITAL

THE DIETARY TREATMENT OF UNDERNUTRITION

THE realization that undernutrition paves the way for various diseases has led in the past few years to a more intelligent consideration of its treatment. We are concerned, at this time, more specifically with marked underweight not with the loss of weight due to illness or with the type of undernutrition associated with pronounced vitamin deficiency. That the vitamins, however, may play an important part when underweight is advanced is an added consideration for its treatment. There are two types of thin individuals. The type that has always been underweight and the type that has lost weight through overwork or worry and then is unable to regain the weight. The fundamental cause of the condition in these two groups is the same—the intake of energy is less than the output. This brings us to the immediate cause of the lowered food intake, namely, appetite. The individual who has always been thin has not lost his appetite but has unconsciously controlled it according to his energy requirements. He has balanced his intake and output so that his body weight is below normal. The individual, however, who has lost weight due to worry or overwork, has lost his desire to eat. This loss of appetite has usually been preceded by a definite cycle of events, the individual becoming fatigued and then “too tired to eat.” This may or may not be accompanied by some gastric symptoms, such as nausea and gaseous eructations.

days he had a good deal of gastric distress after meals. On one occasion he vomited his evening meal. He began to gain weight immediately. During the first week, in spite of the gastric upset, he gained 5 pounds. He continued to gain weight steadily, until the middle of the fourth week when he had a nasopharyngitis and lost $1\frac{1}{2}$ pounds. He regained this almost immediately. His attitude toward food changed remarkably during the period of observation. At the start he had a definite distaste for food. After six days this ceased and by the tenth day he was hungry and looked forward to his meals. Then he developed a ravenous appetite and toward the latter part of the observations he asked for more food than was included in the diet. He maintained his weight and appetite after the observations were discontinued and when last seen, four months after the diet was started, had lost no weight. The intake and output of fluid was measured in this case and there was a positive water balance (Fig. 60).

Case II.—J. M., medical student, age twenty-seven, height 69 inches. During the four months prior to these observations he had lost 15 pounds. This was brought on by worry over his studies. He did not have an actual distaste for food, as did Case I, but had no appetite. Examination showed

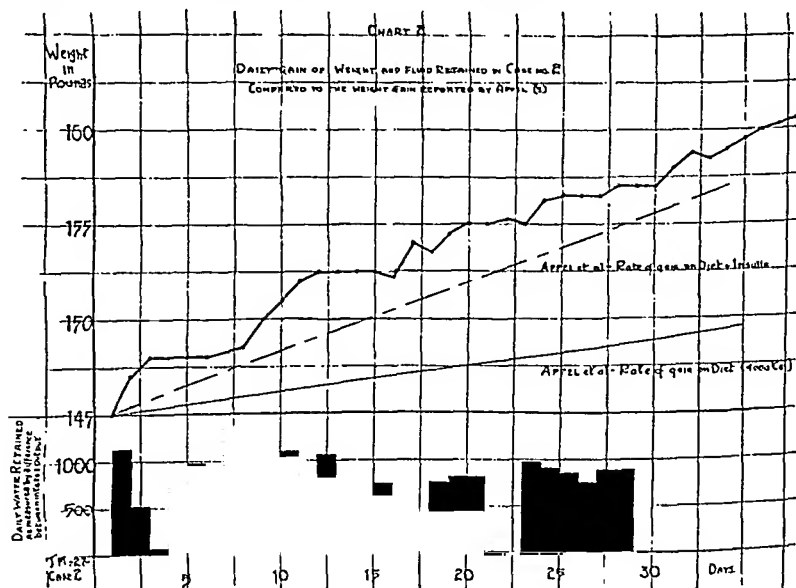


Fig. 61.—Daily gain of weight and fluid retained in Case II, compared to the weight gained as reported by Appel et al.³

an underweight adult. Lungs were clear. x-Ray of the chest was negative. Urine examination was negative. Basal metabolic rate was -10.9 per cent. The blood sugar curve was normal. On a diet of 4400 calories he began to gain weight immediately. He experienced gastric distress after the first three

We are presenting 6 cases of undernutrition, all treated with a high calorie diet and one of which (Case VI) received insulin for a period of time. Three of the cases (I, II, and VI) had lost weight and the other three were patients who had always been underweight and had never been able to gain. Of the six only VI was hospitalized. All the others continued at their work during the period of treatment.

ABSTRACT OF THE CASES

Case I.—R. N., medical student, age thirty-two, height 65 inches. Basal metabolic rate —9.8 per cent. During the six months prior to the period of observation this man had lost 30 pounds. Due to worry and overwork he

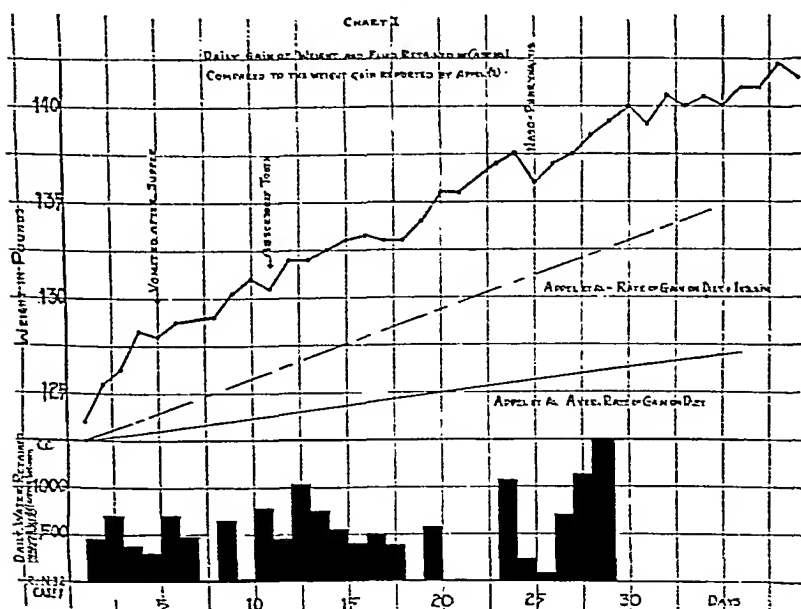


Fig. 60.—Daily gain of weight and fluid retained in Case I, compared to the weight gained as reported by Appel et al.³

lost all desire for food and this was followed by loss of weight. He became extremely tired and in order to get through a day's work he had to rest for at least one hour at noon. Examination showed a poorly nourished adult male, weight $123\frac{1}{2}$ pounds. The lungs were clear and this was corroborated by x-ray examination. The heart was normal. Urine negative. The glucose tolerance test was normal, and is reported with the curves of the other patients. He was placed on a diet of 4400 calories, all of which he ate. For the first ten

count showed 2,530,000 red blood cells, with 68 per cent hemoglobin. The red cells were normal in appearance. White blood cells and differential count were normal. The basal metabolic rate on admission to the ward was -26 per cent, and ranged during the period of observation between -52 and -19 per cent.

He was given a diet of 4000 calories. It was quite obvious that he did not eat all at first, as the nurse often found parts of his diet hidden about his bed and person. He was then kept in bed and made to eat his diet while the nurse

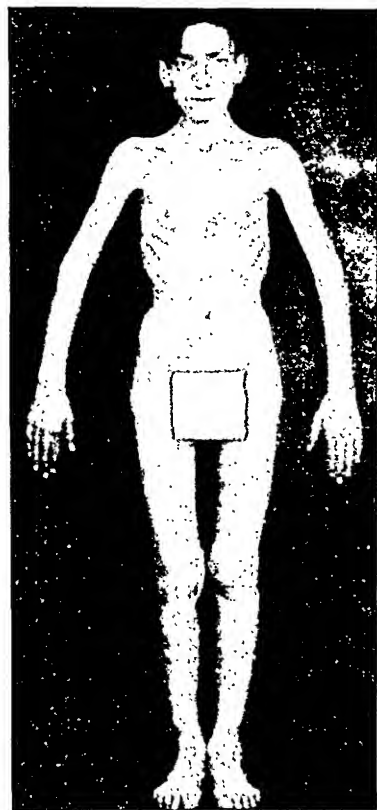


Fig. 62.—Case VI. Before beginning diet.

was watching him. During the twenty-one days of this régime, he gained 13 pounds, an average of 4 pounds per week.

He was then given 5 units of insulin three times a day, twenty minutes before his meals, which was increased in five days to 20 units before each meal. Insulin was continued for eighteen days, during which time there was no increase in his appetite, and only once did he ask for extra food. On the last two days of the insulin period he lost $\frac{3}{4}$ of a pound. If we do not count this

days and did not eat all of the diet, and failed to gain. At this time the gastric discomfort ceased and he ate the entire diet. This was accompanied by a rapid gain of weight, the average being $3\frac{1}{2}$ pounds a week. In this case also the intake and output of fluid was measured and showed a positive water balance. During the next three months he maintained his weight. His appetite, which increased markedly during the period of forced feeding, remained so after he was allowed to eat as he chose (Fig. 61).

Case III.—J. T., a medical student had always been underweight. Physical examination revealed a white male of twenty-three years, weight $164\frac{1}{2}$ pounds, height 74 inches. No abnormal physical findings. x-Ray of the chest was negative. The urine analysis was normal. The blood sugar curve is reported with those of Cases I and II. On a 4400 calorie diet his weight rose from $164\frac{1}{2}$ pounds to 180 pounds in thirty-three days, or an average gain of 3.28 pounds per week.

Case IV.—M. H., a graduate nurse, age twenty-five, who had always been underweight. Physical examination revealed the following: Height, 69 inches; weight, 123 pounds. No abnormal physical findings were noted. The urine was negative, x-ray of the chest was normal, and basal metabolic rate was -11 per cent. On a diet of 4000 calories she began to gain weight. During the first four weeks, she gained 9 pounds, or an average of 2.25 pounds a week. The following week she gained no weight, due to anorexia which accompanied her menstrual period. During the six weeks she gained 11.5 pounds. This gain was maintained when the period of diet ceased.

Case V.—D. L., a graduate nurse, age twenty-eight, who had always been underweight, came under our observation about 20 pounds below the normal for her height and age. Her previous history was normal. Physical examination revealed no abnormal findings. Height, $63\frac{1}{2}$ inches; weight, 103 pounds. x-Ray of the chest was negative as was the urine analysis.

On a diet of 4000 calories she immediately began to gain weight. The gain of weight for the first four weeks was 13 pounds, or an average of 3.25 pounds a week. The following week she was menstruating, and had anorexia for two days, after which she gained 4 pounds more in the last week of observation. Her weight at the end of this period was 120 pounds, which she maintained during the next four months.

Case VI.—A. B., school boy of thirteen years was taken to the Psychopathic Ward by his family because he refused to eat. This complex developed following a tonsillectomy six months previously. Since that time he had lost weight constantly, claimed to have exercised excessively, and eaten little. Physical examination revealed an extremely emaciated boy of thirteen, height 62 inches, weight 83 pounds. The skull was large but not deformed. There were no abnormal physical findings. The urine was negative, Wassermann reaction negative, and the blood sugar determinations ranged from a fasting level of 66 mg. per 100 cc., to 137 mg. two hours after a meal. The blood

daily, after eight days 4 grains were given daily, and four days later 6 grains a day. The basal metabolic rate did not change during this period. In the fourteen days on thyroid he gained 3 more pounds.

RESULTS AND DISCUSSION

Table 1 summarizes the results on these 6 cases. The gain of weight in each case was greatest the first week, averaging 5.2 pounds. During the next three weeks the gain was fairly uniform, varying less than a pound. In the fifth week the rate of gain began to slow and in the sixth week it was definitely less.

TABLE 1

Case number.	Time in weeks.							Total weight gain, pounds.	Time, weeks.	Calories in diet.
	1	2	3	4	5	6	7			
I	5.5	3.5	3.0	3.0	2.5	1.0	..	18.5	6	4434
II	3.5	4.0	2.5	2.0	2.5	1.0	..	15.5	6	4434
III	5.0	2.0	3.75	2.75	3.0	16.5	5	4434
IV	3.5	1.0	1.5	3.0	0	2.5	..	11.5	6	4000
V	4.5	2.0	3.0	2.5	2.5	2.5	..	17	6	4000
VI	9.25	2.75	1.0	5.75	1.5	0	2.25	23.5	8	4000
Aver. gain per week	5.2	2.54	2.46	3.2	2.0	1.5				

The patient who received insulin gained less during the period when insulin was given than during the period of diet alone. As he received 20 units three times daily, a total of 60 units, and as this is as large a dose as has been used by any of the investigators in this country, it should have been sufficient to produce both an increase in appetite and a marked gain in weight (Fig. 64).

In Cases I and II the amount of fluid retained is shown in Figs. 60 and 61. This was not consistently related to the gain in weight.

The average weekly gain for the whole group for six weeks was 2.81 pounds per week. Lueders and Watson⁴ reported a weekly gain of 1.92 pounds weekly over a four-week period giving both diet and insulin. Appel, Farr, and Marshall³ report a gain without insulin of 0.9 pound weekly for a four-week period and of 2.4 pounds weekly when insulin was used, the latter for a period of three weeks. The greatest gain in weight is re-

loss of weight, the gain for the insulin period was 8 pounds, an average of 3 pounds weekly. This was less than when on diet alone.

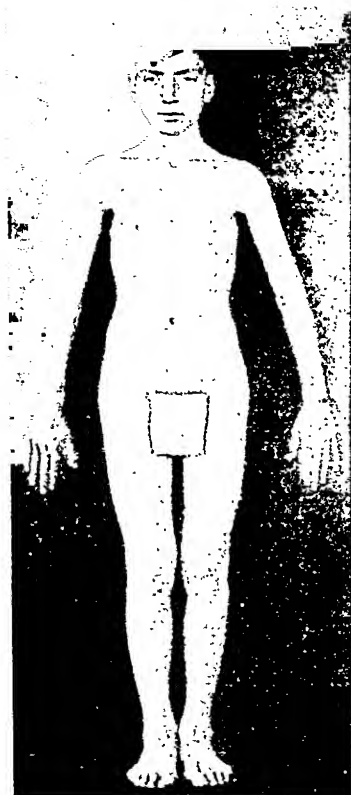


Fig. 63.—Case VI. After the period of diet was completed.

Blood sugars were done after meals during the period of insulin therapy. These were as follows:

Number of days on insulin.	Time of blood sugar.	Blood sugar in mg.
3	2 hours after lunch	105
7	2 hours " "	76
10	2 hours " breakfast	74
13	2 hours " "	69
17	2 hours " "	66

One week after insulin was stopped the blood sugar after lunch was 137 mg. and a week later was 91 mg. after breakfast.

Owing to his constantly low metabolic rate it was decided to begin treatment with thyroid. He was started on desiccated thyroid, 3 grains

The increased intake of food is apparently followed by an increased appetite. The relation of food intake to appetite is also demonstrated on observations on obese patients, who, after a period of decreased diet have a diminished appetite. It is also apparent from our observations that it is easier for the individual who has lost a large amount of weight to regain it, than for the person who has always been underweight to put on weight.

TYPE OF DIET USED IN THE CASES REPORTED

	Amount.	C.	P.	F.	Cals.
Breakfast					
Cereal.....	1 oz.	23	3	0	104
Cream.....	3½ oz.	2	2	20	196
1 glass milk.....	8 oz.	12	8	9	161
Egg.....	One	0	6	6	78
Bacon (crisp) strips (use fat for egg).....	1 oz.	0	3	19	183
Banana or prunes.....	3½ oz.	20	1	0	84
Orange juice.....	6½ oz.	20	1	0	84
Butter.....	1 oz.	0	0	25	225
Bread.....	3 slices	54	9	0	252
Jam or jelly (2 h. tablespoon).....	1 oz.	30	0	0	120
Sugar.....	8 t.	40	0	0	160
Coffee.....	1 cup.	0	0	0	
At 10 A. M.		201	33	79	1647
Cocoa malt with 1 egg and cream or 8 ozs. milk with 1 egg and cream.....	1½ glasses	40	19	36	560
Lunch					
Meat-fish-chicken.....	3½ ozs.	0	20	20	260
Potatoes-rice-spaghetti.....	3½ ozs.	20	2	0	88
Salad { Mayonnaise.....	1 T.	0	0	15	135
15% fruit—2 lettuce leaves.....	3½ ozs.	15	1	0	64
Bread (1 oz. slices) or 1 large roll.....	2 slices	36	6	0	168
Vegetables, 5%.....	3½ ozs.	3	1	0	16
Butter.....	1 oz.	0	0	25	225
Dessert { Pie.....	3½ ozs.	20	4	4	132
Puddings or custard.....					
Ice cream.....					
At 4 P. M.		134	53	100	1648
Cocoa malt with 1 egg and cream (½ glass) or 8 ozs. milk with 1 egg and cream.....	1½ glasses	40	19	36	560
Dinner					
Meat (2 ozs. cheese or 3 eggs).....	3½ ozs.	0	20	20	260
Potato-rice or a creamed vegetable.....	3½ ozs.	20	2	0	88
Butter.....	½ oz.	0	0	12.5	112
Bread (2 slices 1 oz. each).....	2 slices	36	6	0	168
Vegetables, 10%.....	3½ ozs.	6	1	0	28
Dessert (same as noon).....	3½ ozs.	20	4	4	132
		122	57	70.5	1348
Night Meal 10 P. M.					
Veg. for sand.....	3½ ozs.	3	1	0	16
Bread.....	2 slices	36	6	0	168
Mayonnaise or butter.....	½ oz.	0	0	8	72
Milk.....	1 glass	12	8	9	161
or		51	15	17	417
Hershey bar (10-cent bar).....	One	35.8	5.6	24.5	398

Total calories for all meals 5060.

ported by Nahum and Himwich.¹ They observed 4 patients all of whom had lost weight. The period of observation varied from twenty-eight to twelve days. The average gain in weight per week was 5.5 pounds. Insulin was given to all 4 patients. The patients, however, were not subjected to a period of diet alone prior to the use of insulin. It is impossible to know, therefore, how much of this weight could have been gained without the use of insulin. According to our findings the rate of gain is more

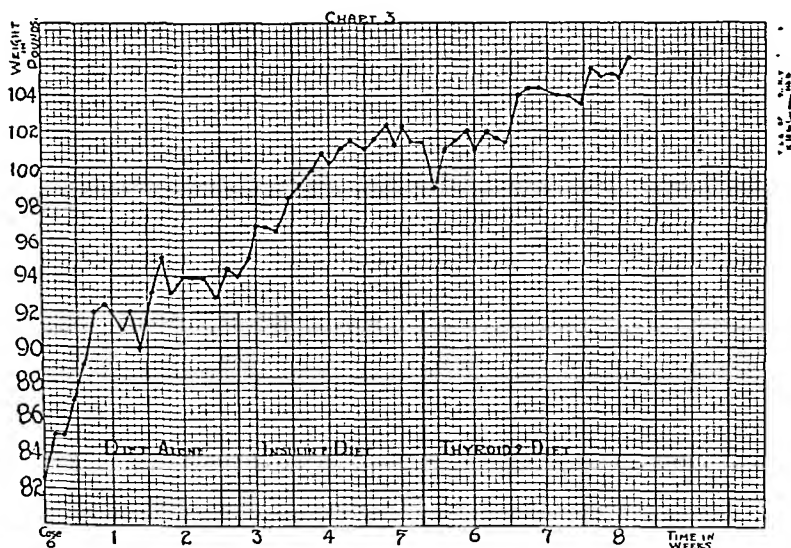


Fig. 64.—Gain of weight in Case VI, on diet alone, diet and insulin, and diet and thyroid.

rapid in the first four weeks. If this is averaged for our group of patients the rate of gain is 3.3 pounds weekly.

These results, we feel, demonstrate the validity of our original premise, namely, that if an individual can exceed in his intake of food his energy output, he will gain weight. The problem of treatment is the problem of stimulating the patient's appetite. Insulin will undoubtedly do this, but it must be used with care and the patients, we think, should be hospitalized or at home for several hours after each meal. In all of our cases the desire for food returned after five or six days of the diet.

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	Amount.	C.	P.	F.	Cals.
Substitutions					
Noon					
Bread.....	(4 ozs.)	72	12	0	336
Mayonnaise or butter.....	1 oz.	0	0	30	270
Meat (ham, salmon or chicken).....	3½ ozs.	0	20	20	260
or					
Cheese.....	2 ozs.				
Cocoa malt or egg malted milk.....	1½ glasses	40	19	36	560
Bananas or 20% fruit.....	Two	40	2	0	168
		152	53	86	1594
Supper					
French toast.....					
Bread.....	5 slices	54 *	9	0	252
Eggs.....	2	0	12	12	156
Butter.....	1 oz.	0	0	25	225
Milk.....	½ c.	5	3	4	68
Sugar.....	2 T's.	30	0	0	120
Jam or jelly.....	2 T's.	30	0	0	120
Cocoa malt or egg malt milk.....	1½ glasses...	40	19	36	560
		159	43	77	1501

Note.—The total caloric value of the diet as reported here is 5060. The total calories consumed by the patients averaged from 4040 to 4000 daily.

TABLE 2

RESULTS OF BLOOD SUGAR CURVES AFTER 100 GM. OF GLUCOSE ON CASES I, II, AND III

Case number.	Fasting.	½ hour.	Mg. of blood sugar.		
			1 hour.	2 hours.	3 hours.
I	91	111	108	88	67
II	97	135	139	132	78
III	92	132	87		62

SUMMARY

Six cases of undernutrition are reported. Three of these had lost weight prior to the period of treatment, and three were individuals who had always been underweight. The 3 patients who had lost weight had also lost their appetite.

All 6 patients gained a substantial amount of weight on a high calorie diet over a period of six weeks. The average gain in weight for this period was 17 pounds.

After a period of diet, in Case VI, insulin was given in doses of 20 units before each meal for a period of three weeks. The rate of gain of weight during this period was not as great as during the period of diet alone.

Procedure.—Four different types of carbohydrate were given to induce the hyperglycemia, glucose, sucrose, invert sugar, and orange juice. In each case 50 Gm. dissolved in 500 cc. of water was given. Fasting specimens of blood, urine, and gastric contents were taken. The patient was then given the carbohydrate dissolved in 500 cc. of water. At one-half, one, two, and three hour intervals, specimens of blood, urine, and gastric contents were again taken. In the experiment with orange juice 500 cc. were given as the carbohydrate contained in this volume of orange juice is approximately 50 Gm., mostly in the form of glucose. The invert sugar was prepared by taking 50 Gm. of sucrose and dissolving it in distilled water. To this 8 drops of concentrated sulphuric acid were added. This was boiled for one minute, allowed to cool, and then neutralized with barium hydroxide. The solution was filtered and the filtrate made up to 500 cc.

The total acidity of the gastric contents was determined by Topfer's method and is reported in cc. of N/10 HCl. The blood sugar was done on the blood filtrate by the Folin-Wu method.² The CO₂ combining power was done on the blood plasma by the Van Slyke gasometric method.³ Benedict's⁴ qualitative and quantitative methods were used for determining urine sugar. Acetone was determined in the urine by Rothera's method.⁵ The total titratable acidity of the urine was done by a modification of the Folin method.⁶

Results.—In Case 1 two curves are reported following the administration of orange juice. The first curve was done when the patient had been on diet and insulin only one week, and it was felt that the fall in plasma CO₂ might be due to the short duration of his treatment. The observations were repeated after a period of six months and the CO₂ remained within normal limits. Cases 2 and 3 had been on diet and insulin for several months prior to the experiments and Case 4 for one month. On Cases 5, 6, and 7, curves were only done following sucrose.

Table 1 gives the results on Cases 1, 2, 3, and 4, on whom comparative curves were done and on one normal adult who was given sucrose. Table 2 gives the results on the cases on

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METABOLISM CLINICS OF THE UNIVERSITY AND BELLEVUE HOSPITAL MEDICAL COLLEGE, NEW YORK UNIVERSITY, AND THE THIRD (NEW YORK UNIVERSITY) MEDICAL DIVISION, BELLEVUE HOSPITAL

THE RELATION OF ACUTE HYPERGLYCEMIA TO THE
CO₂ COMBINING POWER OF THE BLOOD PLASMA
IN PATIENTS WITH DIABETES MELLITUS

In observing groups of severe diabetic patients, it is apparent that despite the use of insulin, there are times during the day when these patients may have a marked hyperglycemia. This is usually of short duration if proper amounts of insulin are used, but in the presence of even mild complications the duration of these hyperglycemic phases is prolonged.

With this in mind we observed a group of patients to determine if hyperglycemia, per se, had any immediate effect on the CO₂ combining power of the blood. As changes in the alkali reserve cause an increase in the total titratable acidity of the urine, the latter was also estimated for the experimental period. Hubbard and Munford¹ have shown the alkaline tide in the urine following meals to be due to the secretion of the hydrochloric acid in the gastric juice. This means a possible change in the carbonic acid-bicarbonate ratio of the blood, and for this reason we also determined the gastric acidity during the period of acute hyperglycemia.

The subjects were diabetic patients treated on the Third (New York University) Medical Division, Bellevue Hospital, and in the Diabetic Clinics of the University and Bellevue Hospital Medical College, New York University.

TABLE 2

EFFECT OF SUCROSE ON THE BLOOD SUGAR, CO₂ COMBINING POWER, GASTRIC AND URINE ACIDITY, URINE VOLUME, AND SUGAR

CASE NO.	BLOOD SUGAR MGMS.					CO ₂ COMBINING POWER					GASTRIC ACIDITY N/10 HCL.				
	CONT.	1/2 HR.	1 HR.	2 HR.	3 HR.	CONT.	1/2 HR.	1 HR.	2 HR.	3 HR.	CONT.	1/2 HR.	1 HR.	2 HR.	3 HR.
5	550	375	417	541	500	68	47.5	49.5	48	55	16	38	55	42	45
6	541	441	455	405	375	55	56	46	51	54	19	78	25	51	71
7	417	556	556	556	500	49	42	—	51	55	21	78	25	—	—

CASE NO.	URINE ACIDITY N/10 HCL.					URINE VOLUME - CC						URINE SUGAR - GRAMS					
	CONT.	1/2 HR.	1 HR.	2 HR.	3 HR.	CONT.	1/2 HR.	1 HR.	2 HR.	3 HR.	TOTAL	CONT.	1/2 HR.	1 HR.	2 HR.	3 HR.	TOTAL
5	2	14	17	27	46	20	15	50	21	14	70	.17	.18	.4	.6	0	1.2
6	31	4	0	4	8	155	70	0	62	36	119	4.6	1.	0	4.	7.7	7.7
7	31	45	2	49	7	97	139	155	150	768	590	1.9	5.6	6.7	10	5.5	27.8

whom curves were done on sucrose only. The height of the hyperglycemia was greatest in Cases 2 and 3 following orange juice. In both of these cases on the day the curve was done with orange juice, the fasting blood sugar was higher than at the time the other curves were done. The CO₂ combining power remained within normal limits following glucose, invert sugar and orange juice, with the one exception, that of curve

TABLE 3

PERCENTAGE FALL IN CO₂ COMBINING POWER FOLLOWING SUCROSE

CASE	CONTROL	1/2 HR.	1 HR.	2 HR.	3 HR.	PERCENTAGE FALL IN CO ₂
# 1	57	40	32	44	48	44% FALL IN 1 HR.
# 2	40	32	54	56	42	20% IN 1/2 HOUR
# 3	57.5	55	54.5	52	54.5	15% IN 2 HOURS
# 4	64	61	59	58	50	12.5% IN 1 HOUR
# 5	68	47.5	48.5	48	55	29.5% IN 2 HOURS
# 6	58	56	46	51	54	20.6% IN 1 HOUR
# 7	49	42	—	51	55	

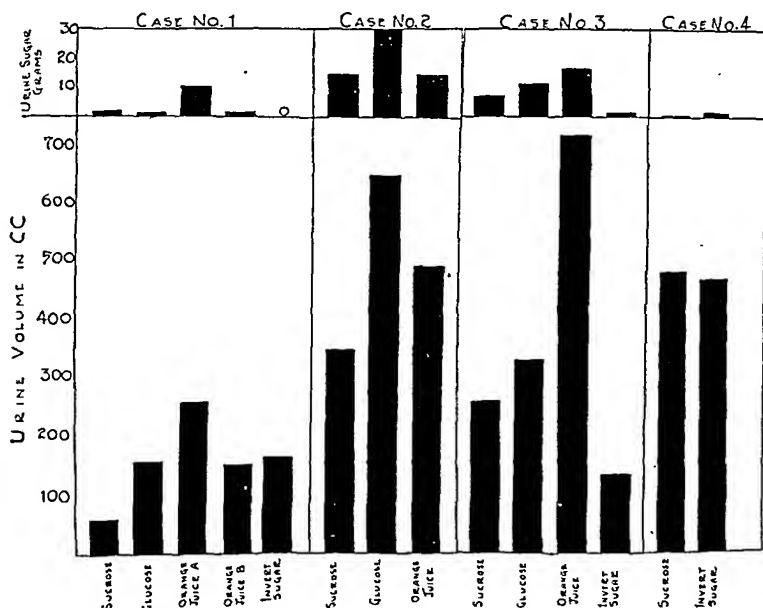
"A" in Case 1, which, as already mentioned, was done early in the treatment of the diabetes. Despite this factor the CO₂ did not show the marked drop that accompanied the ingestion of sucrose. Table 3 shows the percentage fall in the CO₂ combining power in each case after the ingestion of sucrose. In Case 1 the CO₂ fell after sucrose to 32 volume per cent at the first

SUCROSE - 50 GRAMS AND 500cc WATER

DATE	BLOOD SUGAR MG. %			CO ₂ COMP. POWER VOL. %			TOTAL ALKALIC PHOSPH. M/LD WCT.			GRAPE VOLUME CC.			TOTAL			GRAPE OF PIPER			WATER LEFTOVER			SPRING ACIDITY CC. M/LD WCT.		
	CONST.	1/2 HR.	3 HR.	CONST.	1/2 HR.	3 HR.	CONST.	1/2 HR.	3 HR.	CONST.	1/2 HR.	3 HR.	CONST.	1/2 HR.	3 HR.	CONST.	1/2 HR.	3 HR.	CONST.	1/2 HR.	3 HR.	CONST.	1/2 HR.	3 HR.
# 1	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 2	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 3	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 4	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 5	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 6	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 7	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 8	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 9	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 10	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 11	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 12	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 13	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 14	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 15	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 16	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 17	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 18	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 19	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 20	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 21	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 22	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 23	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 24	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 25	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 26	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 27	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 28	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 29	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 30	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
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# 32	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 33	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 34	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 35	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 36	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 37	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 38	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 39	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 40	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 41	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 42	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 43	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 44	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 45	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 46	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 47	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 48	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 49	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 50	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 51	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 52	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 53	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 54	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 55	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 56	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 57	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 58	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 59	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 60	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 61	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 62	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 63	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 64	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 65	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 66	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 67	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 68	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0
# 69	141	232	400	577	40	53	49	28	13	44	20	43	14	18	64	0	0	0	0	0	0	0	0	0

CHART 2

THE EFFECT OF THE VARIOUS CARBOHYDRATES ON THE VOLUME OF URINE



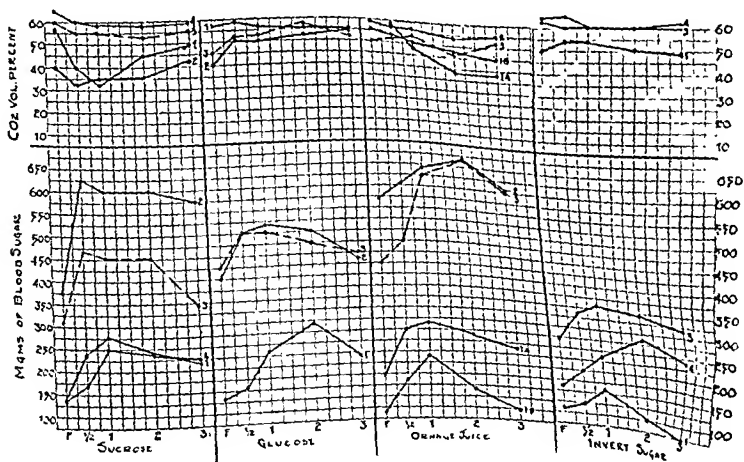
Discussion.—The explanation of the lowering of the CO_2 after the administration of sucrose is found in a paper by Campbell and Maltby.⁷ They observed that dihydroxyacetone, fructose, and cane sugar caused a lowering of the carbon dioxide combining power and a rise in the blood lactic acid. Glucose did not do this. As these changes took place at the proper time to cause stimulation of respiration an increased elimination of CO_2 occurred. Blood dilution would, of course, not explain the fall. Allen and Wishart⁸ working on dogs found a rise in the CO_2 combining power at the time when there was a definite dilution of the blood. McClendon⁹ in experiments on men, giving 50 Gm. of glucose and 1 Kg. of water at the start of his experiments and repeating the glucose with 200 cc. of water at the end of each hour, got a gradual change in blood volume. At the end of one hour, after giving twice the amount of water that we did there was no significant change in blood volume. In our observations the CO_2 had risen again by the third hour,

hour, a drop of 44 per cent. In Case 2 the CO_2 fell to 32 volume per cent at the half hour, in this instance a drop of 20 per cent. Because of this fall in the CO_2 following sucrose, invert sugar was given to Cases 1, 3, and 4 to ascertain whether the hydrolysis of the sucrose which is necessary before the latter can be absorbed by the body, was a factor in this lowering. In none of the cases where invert sugar was used was there any marked change in the CO_2 .

Our results do not show any relation between the urine acidity and gastric acidity, nor do these bear any relation to the changes

CHART 1

THE EFFECT OF HYPERGLYCEMIA PRODUCED BY THE VARIOUS CARBOHYDRATES ON THE CO_2 COMBINING POWER OF THE BLOOD PLASMA



in the CO_2 combining power. It was interesting to note that following orange juice and glucose, we were unable to get any gastric juice for analyses in Cases 2 and 3 after the first half hour and hour. Evidently this tends to pass more rapidly through the stomach than do the other carbohydrates in solution.

The various types of sugar did seem to have a definite effect on the volume of urine excreted. Chart 2 shows that the increased diuresis was in each case associated with an increased excretion of sugar. The diuresis and the glycosuria was least in each case following sucrose and invert sugar.

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which from McClendon's observations would correspond with the time when the blood volume was beginning to show an increase.

The hyperglycemia following the various carbohydrates does not account for the diuresis, but the glycosuria does bear a definite relation to the volume of urine excreted. There are several factors which must be considered in a discussion of the cause of this difference in the urine volumes in these cases. Rioch¹⁰ working on dogs found that after the administration of water by mouth, the curve of diuresis followed the changes of the electrolytes. He felt that the dilution of the electrolytic concentration of the blood was probably the responsible factor in instigating a water diuresis. Priestly¹¹ working on humans suggested that water diuresis is due to the hypotonicity of the blood plasma. Cori¹² has shown that the monosaccharides and disaccharides are absorbed more quickly into the circulation than are the polysaccharides. One might suggest, therefore, that as glucose and the carbohydrate in orange juice are simpler saccharides than sucrose, that they were absorbed more quickly and in consequence there was a more immediate dilution of the electrolytic concentration of the blood with a resulting diuresis during the experimental period. It is also probable that sucrose passes into the intestine more slowly and that this is the reason for the slower absorption. This latter explanation is supported by the fact that no gastric contents were obtained in 2 cases one hour after orange juice and glucose.

Conclusions.—From these results it would seem that hyperglycemia, in an uncomplicated diabetic, has no influence on the CO_2 combining power of the blood. Sucrose, however, may affect the CO_2 combining power. For this reason the simpler carbohydrates are preferable to sucrose as a source of carbohydrate for diabetic patients.

A greater volume of urine was passed following the ingestion of glucose or orange juice than following sucrose.

None of the carbohydrates used had any significant effect on the gastric acidity of the total acidity of the urine, even when the CO_2 combining power of the blood plasma fell.

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SYMPOSIUM ON BLOOD DYSCRASIAS

DISEASES of the blood-forming organs are being encountered with increasing frequency. The group of cases presented in this symposium have been collected from the services of the general hospitals and are of a character that may well be met with in the work of any practitioner of medicine.

The following clinics are included in the Symposium:

Arthur R. Elliott and Edward L. Jenkinson: THE LEUKEMIC STATES: THEIR TREATMENT WITH x-RAY.

Frederick Tice and Richard H. Jaffé: AGRANULOCYTOSIS; SEPSIS LENTA WITH APLASTIC ANEMIC BLOOD PICTURE; ACUTE STEM CELL LEUKEMIA.

Carroll L. Birch: HEMOPHILIA.

LeRoy Hendrick Sloan: POLYCYTHEMIA.

Evans W. Pernokis: APLASTIC ANEMIA.

cytic infiltration of the blood suggests to these protagonists the likeness of the blood to a connective tissue with a fluid matrix, but this idea is discredited by the newer physiology of blood formation with the modern understanding of leukemia as a disease not of the blood but of the blood-forming organs. The idea persists, however, that the leukemic state is merely a phase of circulating metastases from lymphosarcoma. This implies that all patients with leukemia present the condition of lymphosarcoma earlier in their histories, that condition not having perhaps become evident because of the deep location of the involved lymph nodes. In support of this there are arrayed¹ certain cases (fifteen recorded in literature) of patients who, after deep roentgen therapy, developed acute leukemic reactions. Usually from five to ten therapeutic exposures were given. The interval separating the last exposure from the acute blood phase varied from one to five months with an average interval of approximately nine weeks. Whether this coincidence represents an actual cause and effect sequence or merely exemplification of the well-known power of deep roentgen exposures to profoundly alter the functions of the hematopoietic organs remains an open question.

It is difficult to explain satisfactorily the efficacy of roentgen therapy in the suppression of certain of the essential manifestations of leukemia with the contrasting corollary of its inability to materially alter the clinical course or greatly postpone its termination. In this respect there does exist a certain analogy to malignant neoplasms. In a recent communication Hoffman and Craver² analyze their results in 82 cases treated with x -ray. The average duration of life after diagnosis was 3.36 years, which is only four months longer than the average survival of Minot's series of 51 nonirradiated cases. The average duration of life after beginning radiotherapy was 2.62 years. These observers conclude from their experience that irradiation early in the clinical course of the disease made no difference in the average duration of life. For its effect on the prognosis,

¹ Kato and Brunschwig: Arch. Int. Med., vol. 51, No. 1, January, 1933.

² Jour. Amer. Med. Assoc., 97, 12, 836.

CLINIC OF DRS. ARTHUR R. ELLIOTT
AND EDWARD L. JENKINSON

ST. LUKE'S HOSPITAL

THE LEUKEMIC STATES: THEIR TREATMENT WITH
x-RAY

MARKED improvement in the clinical condition of the leukemic patient with subsidence of organ enlargement and reversal of the blood status toward the normal may occur in three ways. It may come about spontaneously without apparent cause (Gosio reports a drop of 150,000 leukocytes in forty-eight hours); it may result from an intercurrent acute infection; it may follow therapeutic effort, especially x-ray irradiation.

It is with the effect of x-ray therapy on leukemic states and especially on myelogenous leukemia that the present discussion is concerned.

The essential cause and pathogenesis of the leukemic states still await definition. There are those who ascribe the condition to infection, implying that it is essentially an infective reaction on the part of the hematopoietic apparatus. They advance no convincing proof in support of their theory, relying mainly upon the rather flimsy structure of analogy. For example, they instance the remissions and exacerbations of the disease and especially its tendency to progress rather abruptly into an acute stage and also its invariable termination as an acute and often fulminating process. The other outstanding theory of its nature is that the essence of the disease is neoplastic but the proponents of this idea are also unsatisfactorily indefinite. The only incident available for the support of this contention appears to be the coexistence in certain rare cases of tumor-like formations of a kind in the bone marrow but these growths have not as yet been identified as leukemic. The leuko-

blasts and lymphoblasts causes these cells to reproduce similarly to myeloblasts. When the cells are more mature (medium- and small-sized lymphocytes) the x -ray stimulates them to grow old and be excreted. If roentgen therapy is used when primitive types of cells are a prominent feature of the peripheral blood, these cells increase in number and the condition of the patient is aggravated in consequence. If employed when blast cells are not apparent in any considerable numbers in the blood smear, there follows a decline in the total leukocyte count because partially matured cells are hastened forward in their development and larger numbers are consequently excreted through the mucous membranes with resulting fall in total leukocyte count and improvement in the patient's condition.

Isaacs adduces as proof of these contentions the fact that the number of leukocytes in the saliva which ordinarily number from 5 to 150 per cubic centimeter will, after an effective x -ray treatment, very rapidly increase to as high as 1500 or even much higher. He affirms that this salivary leukocytosis represents what goes on along the entire gastro-intestinal tract, lymphocytes being mainly excreted through the intestinal mucosa. In the light of these claims it is easy to understand why the x -ray is in appropriate cases so strikingly effective in reducing the total leukocyte count. Whereas practical experience appears to bear out the contentions of this attractive theory, the matter is somewhat confused by occasional inconsistent results. While it is generally conceded that significant relative increase of immature primitive cells in the blood in leukemia is an indication of increasing virulence in the morbid process and that such cases are apt to prove refractory to irradiation, it is not an exceptional thing in practical experience to see the blast cells sharply reduced after x -ray treatment. Piney in a recent reported case¹ noted a reduction in the number of myeloblasts from 47 to 14.4 per cent. So good an observer as Leddy² states that "as a result of their great sensitiveness (to irradiation) the number of immature cells of the myeloblastic

¹ Brit. Jour. Rad., vol. 5, p. 289, April, 1932.

² Amer. Jour. Roent., vol. 21, No. 3, p. 250.

roentgenotherapy gains little justification from these figures and from general experience with its employment, but for its effect upon the general comfort and efficiency of the average patient great credit accrues to this form of treatment and furnishes ample justification for its use. Hoffman and Craver estimated that the average duration of efficient life was 30 per cent greater than in Minot's series, the highest duration being secured where treatment was begun early in the case. The average length of efficient life after beginning treatment was 2.13 years, this representing an average gain of ten months of efficient life. At the present writing we are forced to conclude that, despite any and all forms of treatment, leukemia is incurable; that its clinical course cannot be extended beyond a certain limited period; that, no matter how brilliant irradiation may appear to be in its control, it does not succeed in greatly postponing the inevitable fatal termination. The justification for its employment is its promotion of the patient's efficiency, enabling the individual who otherwise would be a hopeless invalid to continue life's activities.

Isaacs¹ has formulated a brilliant and fascinating interpretation of the effects of roentgen irradiation on the leukemias. Briefly summarized, his contention is that the acute phases of the leukemic state are due to a wandering into the blood stream of embryonic types (premyeloblasts) which in health do not reach the blood stream in appreciable numbers. These embryonic cells, when stimulated by radiation, divide by mitosis, having not yet acquired the ability to mature under stimulation. At a later age, having reached the period of development called "myelocyte," they lose the power of cell division and under stimulation are hurried along through the subsequent stages of maturation to become finally polymorphonuclear neutrophils and presently, having fulfilled their life history and performed their function, will then be excreted by migration through the mucous membrane of the gastro-intestinal tract. These considerations apply equally to cells of the lymphoid series in lymphatic types of leukemia. Irradiation of primitive lympho-

¹ Arch. Int. Med., vol. 50, No. 6, December, 1932.

nail with full force by employing the maximum method of treatment. Therapeutic stimulation of such intensity appears to exhaust the capacity of the organism to respond so that it becomes progressively less effectual and the patient requires larger and larger dosage. Gulland even asserts that the more energetically a case is treated the more certain it is to become refractory. To use much x-ray is to waste valuable ammunition. Its employment should be reserved for the accomplishment of a certain definite purpose at a time when most needed and, when used, it should be in the smallest effective dosage. This last comment will prove an unforgettable admonition to anyone who has inadvertently given a leukemic patient too much radiation. He will then know how deadly a weapon he is handling, capable of killing his patient by producing exhaustion of the blood-forming functions through overstimulation. It is, of course, no condemnation of this valuable therapeutic agency to dwell upon its incidental harmfulness. In smaller measure the same thing may be said of benzol and arsenic. It would be difficult to name a disease the victims of which are more susceptible to disturbance by ill-regulated therapy.

In a broad sense, cases of leukemia fall into two groups with respect to x-ray therapy, *i.e.*, amenable or refractory. Certain clinical criteria exist that, although not altogether accurate, may be employed to inform us as to which group any individual patient belongs. We have mentioned one and perhaps the most important of these criteria, namely, the presence of blast cells in numbers in the blood smear. Other signs of more clinical type are the presence of fever, the coexistence of anemia, especially when it is of increasing grade, the occurrence of purpura, elevation of metabolism, and the general condition of the patient. Any neglect by the therapist of the importance of these signs may lead his patient deeper into difficulty. The development of secondary anemia of progressive type and likewise of purpura (thrombopenia) is bound up with the progression of leukemia very definitely but in a manner not yet fully understood. It is presumed that the inordinate hyperplasia of leukoblastic tissue depresses all other hematopoietic functions by a process, as it

series in the blood may drop as much as 100,000 for each cubic centimeter with a corresponding decrease in the spleen and improvement in the general condition."

Moreover, if the salivary leukocyte count actually constitutes an index of the effects of radiation, then so simple a technic might be convincingly employed in any given case. Unfortunately, we have not been able to confirm these observations with any degree of consistency. We have followed the saliva attentively in treated cases but very little information has been gained from that source, enabling us to gauge the effects of irradiation on the leukocytes.

The fact should not be lost sight of that a high leukocyte count is not an invariable feature of leukemia. It is not the total number of leukocytes in the peripheral blood that necessarily makes for or against the existence of leukemia. The true criterion is the character of the white cells present in the blood smear. It is true as a general statement that once the blood has assumed the cellular characteristics of leukemia it never thereafter loses them. Once a leukemic, always a leukemic, and at no time, no matter how brilliant may x-ray control appear to be, will a careful examination of the blood smear fail to reveal continued cellular pathology. Warthin believed that roentgen therapy merely resolves the leukemic state into an aleukemic one and that the essential disease process (hyperplasia of leukoblastic tissue) is still present—the disease is not cured.

Certain facts should always be borne in mind in our therapeutic approach to leukemia. First and perhaps most important, because it is so apt to be lost sight of through the fascination that the most prominent manifestations of the disease exert upon us, is that a high leukocyte count rising even to 100,000 and over does not necessarily imply that the disease is active or the patient in need of x-ray treatment. It is by no means unusual to have a patient assert a sense of well-being with a white count of over 100,000. On the other hand, patients with a low total leukocyte count (aleukemic leukemia) may be asthenic and inefficient. In using radiotherapy one is hitting the

49 per cent, leukocytes, 372,000, of which 50 per cent were polymorphonuclears, 3 per cent lymphocytes, 3 per cent eosinophils, 2 per cent basophils, 27 per cent myelocytes, 4 per cent band cells. She responded satisfactorily to x-ray therapy, her count thirty days after first treatment being 4,700,000, hemoglobin 65 per cent, and total leukocyte count 18,250 with 18 per cent myelocytes. Unfortunately, not content with this satisfactory effect, we made the mistake of administering one further additional short application "for full measure." The white blood cell count one week thereafter had fallen to 16,050 and after the lapse of another week stood at 6000 with a red count of 3,830,000 and hemoglobin 55 per cent. Ten days later the red cells were 1,910,000, hemoglobin 40 per cent, and leukocytes 1350. Meanwhile the patient had severe hemorrhages from the nose and uterus, and was greatly prostrated. One transfusion of 750 cc. whole blood was given. Very slowly the patient recovered but four months elapsed before the anemia had disappeared and the blood count returned to its former level.

We have learned from our experience to be very guarded in prognosis. The apparent good general health and efficiency of the patient and even a satisfactory blood-showing do not constitute a reliable guarantee of what may transpire at any time even within a few days. Rarely can these transformations in clinical course be satisfactorily explained, although one turns naturally to the idea of infection because of the usual presence of fever. The terminal stage is ushered in by fever (it may reach high levels), increasing debility, and the appearance of blast types of cells. Patients who have been systematically treated with x-ray, perhaps with excellent results, usually succumb after the development of leukoblastosis. Hemoglobinemia is also of value in forming a prognosis, although less important and reliable than fever and blastosis. Patients with low hemoglobin usually respond less satisfactorily to treatment than those with the blood nearer normal in this respect. Experience proves, however, that the fact that the hemoglobin is low does not mitigate against the possibility of improvement provided other findings are favorable. Anemic patients may return to normal after irradiation, proper diet and hematinics. In this manner a patient who received three x-ray treatments covering a period of two weeks showed a gain in blood count from 3,456,000 and hemoglobin 55 per cent to 4,200,000 and 70 per cent with a decline of leukocytes from 80,000 to 10,200 within ten weeks. It is difficult to account for the fact that the dis-

were, of overcrowding and as a consequence red cell and blood platelet formation falls more or less rapidly. However this may be, there can be no doubt that the development of anemia and hemorrhagic manifestations constitute unfavorable indications, are usually associated with fever, myeloblastosis, elevation of the metabolism rate, decline in weight and the development of asthenia, all constituting together a clinical picture which, according to degree, warns us of progression and activity in the leukemic state and discounts the availability of roentgen therapy. A good rule to follow is to keep the patient equally with disease manifestations in mind in deciding how far to push treatment. As accurately as it may be regulated, just the right amount and no more x-ray should be administered to keep the patient in optimal condition. Too heavy or too frequent applications may so inhibit hematopoiesis as to bring about not only serious leukopenia but general all-around aplastic anemia.

We insist upon careful examination of the blood and especially of the blood smear and a consideration of the other criteria mentioned before deciding whether roentgen therapy shall be used or not. We insist, moreover, that blood examination should be invariably made before each and every treatment and that the interval between applications and the x-ray dosage be regulated in inverse ratio to the fall in leukocyte count: the greater the drop, the shorter the x-ray application and the longer the interval between sessions. What the line of safety may be beyond which no further attempt should be made to reduce the total leukocyte count may perhaps vary according to the individual therapist's experience, but all will agree that a rapidly falling leukocyte count should be watched carefully and with concern and that when the total count has reached 50,000, utmost caution becomes necessary in the administration of additional radiation. We do not consider that further x-ray treatment is safe or advisable after the count has dropped to 40,000. What may follow neglect of this precaution is strikingly illustrated by the following case history.

The patient, a white female, aged forty-eight, had been under observation for a year. The first blood count showed erythrocytes, 2,450,000; hemoglobin,

rather heavy dosage. We feel sure that a large, soft spleen is more favorable and much easier to cope with than a hard spleen. It is not necessary to directly treat the spleen in order to reduce its size. In favorable cases irradiation over the chest will cause a satisfactory reduction in the size of the spleen. Reduced in this way it does not become hard and shrunken. In this manner we conclude that it is possible to preserve, in some measure whatever advantage to the blood situation is represented by the splenic functions. The red bone marrow is the chief depot for the production of blood elements and the ribs, scapulae vertebrae and pelvis contain red marrow in adult life. Treating over the long bones, especially the tibiae, fibulae, ulnae and radii, we believe accomplishes very little, inasmuch as there is not much blood-producing marrow in these bones after puberty. The chest contains a great deal of blood and we feel that direct irradiation of the blood is an important factor in bringing about ripening of partially matured leukocytes. These different considerations have led us to abandon the older form of cross-fire over the spleen and we now treat the chest front and back. To avoid irritating the spleen, any treatment directed toward that organ is brief in duration and only over a portion of the organ.

We have established the following program in giving x -ray to leukemic patients. The patient's general clinical condition is fully recorded and the blood completely examined with a differential count of 200 cells. If all seems clear to go ahead, the chest is treated posteriorly, using 150 to 200 roentgen units at 200 kvp. with $\frac{3}{4}$ copper and 1 aluminum of filter. Blood counts are made every other day and, as long as the leukocyte count is falling, no further treatment is given. When the count becomes stationary at an unsatisfactory level or begins to increase, further treatment is administered, using the same factors and procedure until the count is reduced to about 40,000. In pursuance of a definite policy of giving these patients as little x -ray as is necessary to bring about the desired result, we withhold further irradiation after about 40,000 white blood cells per cubic centimeter is reached. In such a policy we have in mind the occasional continuing or postponed effect of the rays

ease may often run into a quiescent stage. This does not necessarily follow x-ray therapy because it was noticed before radiotherapy became available. This spontaneous remission has its analogy in other blood dyscrasias. Vigilance should not be relaxed during this phase of the disease because the blood smear still shows that the disease is present and the spleen may be enlarged.

Enlargement of the spleen has been a prominent feature in most of our cases. At times its mere size has been the cause of upper abdominal distress and digestive disturbance, probably through pressure. The fluoroscope may show considerable displacement of the hollow organs. The spleen is often tender to pressure. We have a very definite opinion that the consistency of the spleen, so far as it can be made out by palpation, serves as an indication of some value in splenomegalic cases regarding the effects to be expected from irradiation. When the spleen appears to be soft, we have reason from experience to expect better results than when it is hard to the feel and of only moderate size. The spleen is assumed to take part in both leukogenesis and leukolysis. Its function should be preserved so far as is possible, in the interests of the leukemic patient. The application of the x-ray directly to the spleen by the system of cross-firing will reduce its size and make the organ hard. It is doubtful that these effects represent an advantage. On the contrary, it has seemed to us that patients who have had the spleen shrunken and hardened by intensive irradiation have made less satisfactory progress than when the spleen has been spared. In the early days of roentgen therapy we employed cross-fire applications over the spleen. It is true that the spleen usually became smaller and the count decreased in number with improvement in the differential formula. We have been impressed with the fact that the drop was too sudden and at times proved uncontrolled so that a dangerous leukopenia supervened. It has been our experience to see the spleen rapidly decrease in size at first but later grow large again and become hard. Each succeeding treatment finds the spleen more resistant to irradiation so that very little effect is secured even by

The following brief summary of a case history shows the value of the differential count as a forewarning factor in prognosis.

Case II.—We began x-ray treatment of this patient in January, 1928. The original blood count was erythrocytes 4,070,000, hemoglobin 60 per cent, leukocytes 192,000 with polymorphonuclears 42 per cent, myelocytes 56 per cent, eosinophils 2 per cent. The temperature was normal, spleen enlarged but not hard. Over three years of continuous routine observation with occasional x-ray treatments enabled us to keep this patient in excellent efficiency and satisfactory blood condition. There were never any myeloblasts in the differential counts until August 25, 1931, when they numbered 9 per cent. There was as yet no fever but the spleen had enlarged considerably and was so tender that the patient was unable to lie on her left side. The appearance of myeloblasts was accompanied by sudden increase in the total leukocyte count to 120,000. Three weeks before it had been 20,400 with 12 per cent myelocytes and no blast cells.

It has seemed to us that an occasional sharp increase in the total white count is not necessarily a bad sign. It demonstrates the ability of the marrow to respond to stimulation, even if the stimulus be a morbid one. It opens up the chance for further response to x-ray therapy, whereas a low and falling white count closes the door to further control. Added to this, if myeloblasts drift into the blood picture, the x-ray may become an instrument of harm rather than of good. We ventured to give this patient further roentgen therapy, proceeding very conservatively under strict blood count control. The treatment did her little good. She died six months following the appearance of leukoblastosis.

In closing this discussion we would emphasize the following points. All forms of leukemia are alike incurable and rarely extend beyond a limited period of time. In common with other kinds of therapy the x-rays do not greatly postpone the fatal ending. The x-rays do, however, unquestionably constitute the best means of promoting the efficiency of the patient, enabling him to continue life's activities when otherwise he would be an invalid. In carrying out roentgen therapy our only object, therefore, is to get the patient in efficient and comfortable condition and keep him there as long as possible. For this reason his subjective state and general systemic condition should be taken importantly into account in undertaking and regulating treatment instead of focusing too exclusively on the specific disease manifestations (leukocytosis, splenomegaly, adenopathy, etc.). No more x-ray should be administered than is.

with the hazard of a secondary aplastic anemia. Too heavy dosage may precipitate the same condition that we observe in the terminal stage of the disease when anemia and thrombopenia become the dominant factors.

The following case histories taken from our records illustrate the benefits to be derived from x-ray control, if not in prolongation of life, at least in promotion of efficiency.

Case I.—A male patient, forty years of age, was referred for x-ray therapy and entered the hospital March 27, 1926. His general condition was satisfactory, so that he worked daily at his occupation. His temperature was normal. His chief complaint was abdominal distress. His spleen was very large, filling most of the abdominal cavity. Blood count was—erythrocytes 4,070,000, leukocytes 300,000, hemoglobin 85 per cent; differential count—polymorphonuclears 32 per cent, lymphocytes 10 per cent, myelocytes 58 per cent. Roentgen therapy was instituted and his condition showed prompt improvement. After five treatments separated by rather long intervals between March 29, 1926, and July 15, 1927, the spleen was practically normal in size and his white count 20,800. He did not report again for treatment until April 19, 1929, when his leukocyte count was found to be 220,000 with polymorphonuclears 35 per cent, lymphocytes 3 per cent, basophils 6 per cent, premyelocytes 23 per cent, metamyelocytes 20 per cent, myeloblasts 10 per cent, eosinophil myelocytes 3 per cent. His red cell count was 2,890,000, and hemoglobin 50 per cent. The spleen was again greatly enlarged. There was no fever. Seven x-ray treatments were given over the chest anterior and posterior, alternating, and on June 19, 1929, the count was as follows: Red cells 4,080,000, white cells 6000, hemoglobin 57 per cent; differential count—polymorphonuclears 55 per cent, lymphocytes 13 per cent, monocytes 7 per cent, eosinophils 3 per cent, basophils 5 per cent, metamyelocytes 5 per cent, premyelocytes 1 per cent. No further treatment was administered until February 5, 1930. At this time the hemoglobin was 75 per cent and there were no myeloblasts present in the smear. On November 14, 1930, the blood count was as follows: Erythrocytes 3,710,000, hemoglobin 60 per cent, leukocytes 24,500 with a differential count of polymorphonuclears 25 per cent, metamyelocytes 15 per cent, premyelocytes 20 per cent, eosinophils 2 per cent, basophils 19 per cent, lymphocytes 5 per cent, myeloblasts 14 per cent. At this time the patient was cachectic and weak, and the spleen again very large and tender. It seemed to us a losing game and we demurred against the patient's urgent demands for further treatment, finally complying by giving him four very conservative sessions which, as was to be expected, did not improve his blood count or systemic condition. The last treatment was administered on March 23, 1931. He died April 13, 1931. Over five years elapsed between the first roentgen treatment and the patient's death. During this entire period up to six months before the end, the patient retained his efficiency and satisfactory well-being. We think that this case demonstrates the efficacy of x-ray control and the valuable aid to be secured by differential blood counts in regulating treatment.



necessary to accomplish our object. Lack of conservation in dosage may so depress hematopoiesis as to give rise to serious consequences (aplastic anemia, purpura). Attentive study of the blood smear should precede every application. Leukoblastosis is an unfavorable development and probably indicates the advent of the x-ray refractory stage. Increase of caution should thereafter be the rule. Fever, increasing anemia, hemorrhagic manifestations are other unfavorable signs. A falling blood count contraindicates further radiotherapy until it has again become stabilized. A relatively high total leukocyte count is not necessarily a bad sign, provided no blastosis exists and the patient feels well. Under these conditions, treatment may be withheld and observation continued. We have found irradiation of the chest (ribs, scapulae, vertebrae, and blood mass) more effective in the long run and less hazardous than intensive treatment over the spleen.

speaking and examination of her throat disclosed several large, ulcerated areas in the pharynx and on the base of the tongue, covered by a necrotic, foul-smelling membrane. Her neck was very tender. Otherwise the physical examination was negative.

The general impression was that of a severe septicemia with an ulcerated pharyngitis which made one suspicious of an agranulocytosis.

Blood examination showed hemoglobin 70 per cent, red blood cells 3,700,000 and white blood cells 3500. On smear the first observer reported only lymphocytes. A second person examined a smear and stated that he found 12 per cent young neutrophilic leukocytes. A third person made a differential count and found 68 per cent young leukocytes, all with a single bent or lobulated nucleus. Thus, the idea of an agranulocytosis was discarded and the diagnosis of a severe septicemia retained.

Throat culture revealed *Streptococcus hemolyticus*.

The patient's temperature remained high, never dropping below 101.6 F. and rising to 104 F. several times. She remained toxic and stuporous with persistent throat lesions despite peroxide and perborate gargles and subcutaneous fluids until her death six days after entrance.

After death Dr. Jaffé examined a blood smear and made a differential count of 67.2 per cent monocytes and 32.8 per cent lymphocytes.

DR. JAFFÉ: At the time the autopsy was performed I had not yet seen the blood films but the anatomical changes were so characteristic that I did not hesitate making the diagnosis agranulocytosis. The changes of the oral cavity were most striking. On both sides the lateral margin of the tongue was transformed into irregular ulcers which extended to the floor of the mouth. The floor of the ulcers was covered by a firmly adherent, shaggy, foul-smelling membrane of a dirty brown color and the edges of the ulcers were of similar color and very friable. The mucosa of the pharynx was injected, bright purple-red, and the tonsils were small and flat and discolored reddish-gray. Smears taken from the gangrenous material of the ulcers revealed a great variety of cocci and bacilli and a large number of fusiform bacteria with single fine and thick spirochetes.

The lungs were distended and over the lower lobes the pleura was covered by loosely adherent, thin, light yellow-gray membranes, underneath which the pleura was deeply injected. The lower lobes contained many small hemorrhagic areas of consolidation and the bronchi were filled by a frothy mucoïd material. The heart weighed 345 Gm. The myocardium broke very easily and its color was a light purple-brown mottled with grayish-brown areas. The spleen was enlarged to about double its normal size. It was soft in consistency, the capsule was thin and the sectioned surface exposed a dark purple-red and moist pulp from which the follicles and trabeculae were well differentiated. The liver was markedly swollen, its weight being 2270 Gm. It was so friable that it almost broke on handling. The external aspect and surfaces made by cutting were of a light gray-brown color. The mucosa of the gastro-intestinal tract was pale and in the colon it was slightly edematous. The kidneys felt very soft and after removing the capsule, which was accomplished with little difficulty, a smooth and pale pinkish-gray surface became visible. The cortical marking could not be

CLINICOPATHOLOGIC CONFERENCE ON BLOOD DYSCRASIAS

COOK COUNTY HOSPITAL

AGRANULOCYTOSIS; SEPSIS LENTA WITH APLASTIC ANEMIC BLOOD PICTURE; ACUTE STEM CELL LEUKEMIA

FREDERICK TICE (Clinical Presentation)

AND

RICHARD H. JAFFÉ (Pathologic, Anatomical and
Hematological Discussion)

AGRANULOCYTOSIS

DR. TICE: Mrs. M. B. entered the hospital October 26, 1932, and died on November 1st. The examining room diagnosis was septicemia. Three and one-half weeks before entrance this patient, a colored female, aged thirty-eight, noticed that she began to feel weak and to have pains in both arms and legs. She went to a physician who took a blood test and found that the blood Kahn and Wassermann were positive. At that time she had a temperature of 101.8 F. The doctor gave her a "shot" of neoarsphenamine, then two of mercury oxy-cyanide, a second neoarsphenamine and a third mercury at about two-day intervals. After the last three injections, especially the last one, she had a reaction and was advised to go to the hospital. This she did after a week at home with no improvement.

On entrance to the hospital she complained of shortness of breath and diarrhea, with stiffness of her legs and inability to walk, all of a few days' duration. She had had four pregnancies and two miscarriages, the last one nine months before.

Her husband had been treated for syphilis in 1928 and 1930. She admitted taking alcohol to excess.

Physical examination revealed the patient to be acutely ill; temperature 104 F., pulse 146 and respiratory rate 28. She seemed to have difficulty in

colpitis; hypostatic pneumonia in both lower pulmonary lobes and recent fibrinous pleuritis; severe parenchymatous degeneration of the myocardium, liver and kidneys; nodose goiter.

Agranulocytosis is a well-defined symptom complex but I do not think that it is a disease *sui generis*. In the center of the clinical and anatomical picture there is a severe toxic injury of the bone marrow, in particular of its granulopoietic part. In the early stages the bone marrow is very cellular, indicating an active, proliferative response to an irritating stimulus. The proliferating myelocytes, however, soon undergo degeneration. They lose their granulation, the nuclei become pyknotic and finally the cells break down completely so that, in the later stages, the bone marrow is deprived of the precursors of the leukocytes. The erythropoietic tissue is usually little affected while the megakaryocytes may be either increased or decreased in number. They, too, sometimes show regressive changes.

Similar alterative changes of the myelocytes are occasionally met with in cases of frank septicemia and there are all transitional stages between these cases of septicemia and the classical form of agranulocytosis. Agranulocytosis may be associated with a known infection or intoxication. In the majority of cases the etiology, however, remains obscure. It is possible that we may be dealing with the combination of two factors, namely, a severe irritation of the bone marrow and an inherited or constitutional weakness of the bone marrow which leads to this abnormal and deleterious response. The gangrenous and ulcerative lesions in the mouth, vagina, throat, intestinal tract or skin, which are often associated with the agranulocytosis, are secondary. They are the result of the complete breaking down of the local defense reactions due to the absence of the leukocytes which are so important for the quick prevention of bacterial invasion.

As far as our case is concerned, the arsphenamine medication has to be kept in mind as a possible etiologic factor. I have seen several cases of agranulocytosis following arsphenamine treatment and the literature contains a number of reports dealing with similar observations.

made out. In the vagina there were several irregular ulcers, the largest of which measured 40 x 25 mm. in diameter. The center of these ulcers was covered by an adherent light yellow-gray and soft membrane. Otherwise the genitalia were unchanged.

The bone marrow of the femur was very soft, light yellow-gray with ill-defined, pale purple-gray areas.

After the autopsy I went over the blood films which had been taken during life and I was not able to detect a single neutrophilic leukocyte. The cells which had caused so much controversy proved to be monocytes which were somewhat atypical. The nuclei, namely, were deeply segmented and were often subdivided into several lobules. Because of this lobulation and segmentation, the nuclei resembled those of polymorphonuclear, neutrophilic leukocytes but the cytoplasm showed the bluish-gray coloration characteristic of monocytes and there were only a few azur granules present.

On microscopical examination the bone marrow was found to be very cellular, 70 per cent of it being made up of immature blood cells. There was a great predominance of neutrophilic myelocytes which, however, showed severe degenerative changes in the form of disintegration of the specific granules. The granules seemed to become dissolved into the cytoplasm. Their contours became indistinct and the cytoplasm assumed a diffuse, purple-pink coloration. By this dissolution of the granules nongranulated elements resulted which resembled somewhat myeloblasts save for the nuclei, which were compact and often pyknotic. There were also a few mature leukocytes with similar regressive changes of their granulation. The oxyphilic granulocytes were better preserved but they too revealed breaking up and disappearance of the granules. Twenty-five per cent of the bone marrow cells were nucleated red cells in various stages of maturation. Among the normoblasts there were single very large forms. The megakaryocytes were scanty but well preserved. The cells of the cytoplasmic reticulum were swollen and contained many phagocytosed blood cells.

Around the ulcerations of the mouth and vagina there was not a single leukocyte and the necrotic tissue, which was exceedingly rich in cocci, fused with the living tissue without a definite line of demarcation. Underneath the necrotic zone the capillaries were much dilated and were filled with small round cells and mononuclear elements. In the loosened connective tissue around the blood vessels there were accumulations of lymphocytes and of swollen histiocytes with a vacuolated cytoplasm.

The other organs did not reveal any unusual histologic changes. There was some swelling and dissociation of the liver cells and there was a moderate activation of the Kupffer cells of the liver which displayed erythrophagocytosis. The spleen was engorged with blood and in the pulp there were many large basophilic round cells and plasma cells and a few nucleated red cells. In the kidney the glomerular tufts were of increased cellularity and the lining of the convoluted tubuli was swollen and granular.

The anatomical diagnosis of this case reads as follows: Agranulocytosis; severe toxic injury to the granulopoietic tissue of the bone marrow; gangrenous ulcerative glossitis; ulcerative

and trabeculae were flattened. There were no macroscopical changes on the heart valves. The lungs were moderately distended, anemic and moist. The thyroid contained a small, light yellow node which occupied the lower pole of the right lobe.

The lower pole of the spleen was found 7 cm. below the costal arch. The size of the spleen was more than four times the normal size and the weight was 620 Gm. It cut with little difficulty and the sectioned surface exposed a moist, light purple-gray pulp which was well separated from the pale gray follicles. On the posterior aspect near the upper pole there was a firm, wedge-shaped area located subcapsular and measuring $9 \times 4 \times 3$ mm. in diameter. The color of this area was a light yellow-gray. The liver weighed 1950 Gm. It was moderately firm in consistency and light purple-brown in color. On the sectioned surface an irregular purple-red marking was visible. The gallbladder contained much deep brown bile.

The kidneys together weighed 360 Gm. The surface was pale tan in color and smooth. The cortex measured 10 mm., was pale gray-brown and revealed no structural differentiation. The cavum uteri and the cervical canal contained a small amount of blood-stained mucus. In the right ovary there was a hemorrhagic corpus luteum cyst. The abdominal lymph nodes were swollen, medullary and light purple-gray in color. The bone marrow was soft and reddish-gray.

In view of the blood findings which suggested the clinical diagnosis of aplastic anemia, we shall be particularly interested in the microscopic appearance of the bone marrow. It is of considerable cellularity and much congested, the sinusoids and capillaries being very prominent and engorged with red blood cells. Many well-defined lymph follicles are scattered throughout the marrow. Outside these follicles there is a mixture of myeloid cells, among which nucleated red cells are most prominent. They appear in groups and the erythropoiesis goes back to the most immature forms, to the erythrogonias. There are relatively few neutrophilic myelocytes, the granulations of which show regressive changes similar to those described in the case of agranulocytosis. Some of the myelocytes are necrotic. The megakaryocytes too reveal signs of disintegration starting with loss of the granulation and pyknosis of the nuclei and terminating in necrosis. In addition to these cells there is a moderate number of lymphocytes, plasma cells, monocytoïd elements and a few histiocytes containing engulfed red blood cells. In summary the findings in the bone marrow are characterized by a severe impairment of the granulopoiesis, degeneration of the megakaryocytes, an active erythropoiesis and a hyperplasia of the lymphatic tissue. The changes in the other blood-forming organs (liver, spleen, lymph nodes) consist of a marked activation of the reticulohistiocytic elements which display much erythrophagocytosis, and occasional nests of erythroblasts and normoblasts. In the spleen there are also a few megakaryocytes.

In the kidney the glomeruli are much enlarged. The tufts are very cellular and fill almost completely the Bowman's spaces. Cells with oval nuclei and fine chromatin granules are predominating. The tubular epithelium shows granular swelling with occasional fat droplets near the base. The histologic diagnosis of the renal changes is acute glomerulonephritis.

Of the other histologic findings, those of the myocardium are of importance. Near the larger blood vessels there are nodular accumulations of large mono- and

SEPSIS LENTA WITH APLASTIC ANEMIC BLOOD PICTURE

DR. TICE: Entered October 24, 1932, died October 26, 1932; examining room diagnosis, pneumonia.

About five years ago this patient, Mrs. B., white, aged forty-two, had an attack of multiple arthritis which caused her considerable discomfort. She remained apparently well up to midsummer, at which time she entered the hospital with the clinical symptoms of disturbed cardiac compensation from which she recovered after a month in the hospital. In August she returned with a facial erysipelas and the statement that she had experienced two slight "heart attacks" during the intervening months since she left the hospital. She recovered from the erysipelas and remained apparently well except for an occasional slight attack of syncope. Twenty-four hours before this admission she had a severe chill followed by fever and a marked weakness.

Physical examination showed the patient to be acutely ill; temperature 106 F. rectally, pulse 134 and respiratory rate 30. The general condition of the patient rendered it very difficult or impossible to make a satisfactory examination. She was rather obese, appeared quite anemic, complained of exhaustion and some dyspnea but no pain. The heart was found to be slightly enlarged to the left with a moderate grade apical systolic murmur. No other murmurs could be detected and no arrhythmia. Many large moist râles could be heard over both lung bases with slight impairment of the resonance but no definite areas of consolidation. The abdomen was slightly distended, the liver about four fingers below the costal border with a palpable spleen. No conjunctival, buccal mucous membrane or skin petechiae or purpura were present.

Blood examination showed hemoglobin 50 per cent, red blood cells 1,480,000 and white blood cells 450; marked anisocytosis, poikilocytosis and polychromatophilia. Differential count revealed only large and small lymphocytes, no polymorphonuclears and no nucleated reds or reticulocytes. Platelets were 0.0006 volume per cent, equal to 42,000 platelets per cubic centimeter. Blood cultures were positive for *Streptococcus viridans*.

The examining room diagnosis of pneumonia could hardly be confirmed for lack of findings. The clinical history and cardiac findings were suggestive of a possible bacterial endocarditis but was not conclusively established. Some serious consideration was given to a possible aplastic anemia based on the blood findings.

DR. JAFFÉ: The external examination revealed the body of a slenderly built and fairly well-nourished white woman whose skin was light yellowish-gray in color. The sclerae were slightly icteric and the visible mucous membranes appeared very pale. The fingers of both hands were fixed in flexed position and the interphalangeal and metacarpal joints were deformed by nodular osseous elevations arising from the border of the articular surfaces. Above the symphysis there was a linear scar 13 cm. in length.

The right pleural cavity contained a small amount of clear fluid and the upper lobe of the right lung was in places attached to the wall of the chest. The heart was enlarged, its weight being 365 Gm. The myocardium was light purple-brown and very friable and in the left ventricle the papillary muscles

ever the jaw was moved. With these symptoms there has been a progressive weakness, unassociated with chills, fever or pain. Early this morning there suddenly developed a severe, uncontrollable nosebleed for which he entered the hospital.

At the time of examination the patient's temperature was 97 to 101 F.; pulse 120, respiratory rate 28 to 32. Marked pallor and anemia with subconjunctival and retinal hemorrhages were noted. There were numerous cutaneous petechiae over the entire body but especially in the region of the neck and over the upper portion of the chest. The mucous membrane of the mouth and pharynx presents the same type of lesion.

All of the regional lymphatic glands, the cervical, axillary and inguinal, were enlarged with slight enlargement of the liver. Spleen was not enlarged.

No appreciable enlargement of the heart could be detected. A systolic murmur of moderate degree was heard over the apex and also over the base of the heart.

Many blood counts were made, of which only the first and last will be noted. The first showed hemoglobin 48 to 50 per cent, red blood cells 2,170,000, white blood cells 6500, with a differential count of 90 per cent large and small lymphocytes and 10 per cent polymorphonuclears; platelets 0.0012 volume per cent, equal to 84,000 per cubic centimeter. The last blood count showed hemoglobin 25 per cent, red blood cells 1,460,000 and white blood cells 250,700.

Blood cultures were negative.

Bacterial endocarditis was considered but ruled out on the lack of sufficient findings. As the disease progressed and with additional clinical and laboratory evidence, it became more and more convincing that the primary pathology was a blood dyscrasia, probably some form of a leukemia.

Dr. Jaffé examined one of the blood smears with the diagnosis of a stem cell leukemia.

DR. JAFFÉ: In studying the blood films of this case I found that 92.8 per cent of the white blood cells were lymphoid elements from 10 to 20 micron in diameter. The nuclei of these cells were round and the chromatin formed a fine, dense net the meshes of which were filled by pale stained basophilic material. Nucleoles were not present. The nuclei were surrounded by a narrow rim of a homogeneous, sky-blue cytoplasm (Giemsa-Wright stain). An occasional cell contained small vacuoles. The oxydase reaction was negative. Cytologically these cells are different from lymphoblasts and myeloblasts and represent the most immature type of blood cell which now is usually called "hemocytoblast" (stem cell). There were 0.4 per cent of neutrophilic metamyelocytes, 3.6 per cent neutrophilic leukocytes and 3.2 per cent lymphocytes. There were 8 normoblasts to 250 white cells and 1 erythrogonia was discovered after a long search.

The result of the necropsy confirmed the hematological diagnosis of acute hemocytoblast (stem cell) leukemia. On external examination the breasts were found enlarged. They were semispherical in shape, soft and on sectioning were seen to be composed of a medullary, grayish-white tissue. The subcutaneous lymph nodes were from peanut to cherry size, firm and discrete. In the region of the thymus a firm, lobulated, light gray-brown mass was present which covered the upper third of the pericardial sac and measured 19 x 7 x 3 cm. in diameter. There were recent extravasations of blood underneath the endo-

multinuclear cells with an ample pale stained cytoplasm and with oval nuclei revealing a striking chromatin structure. Namely, the chromatin is concentrated in the axis of the nuclei in the form of an indented rod from which fine branches extend to the nuclear membrane. These cells are arranged about a homogeneous center that stains pink with eosin. The histologic description is that of typical "Aschoff's bodies." There are also a few flame-shaped scars with pale brown pigment granules which in places substitute the muscle fibers. The microscopical examination of the heart valves fails to reveal any abnormal findings.

Cultures taken from the heart's blood and the spleen yielded a pure growth of *Streptococcus viridans*.

The anatomical and, especially, the microscopical findings are those of a long-standing, chronic streptococcic septicemia, of a sepsis lenta. The subicteric discoloration of the skin and sclerae, the large splenic tumor, the generalized activation of the reticulohistiocytic system, the erythrophagocytosis, the anemia, and the injury to the granulopoietic tissue are very characteristic. The acute glomerulonephritis is a very common terminal complication of this condition. Except for the lack of valvular changes and of embolic manifestations the picture is identical with that of subacute bacterial endocarditis (endocarditis lenta) which is but a special form of the prolonged streptococcic septicemia in which the micro-organisms have become settled on the heart valves. The small infarct of the spleen in our case is due to local thrombosis in a group of small splenic arteries. The anatomicohistologic diagnosis is also borne out by the result of the bacteriological examination which disclosed a pure growth of green streptococci, by far the most common cause of the sepsis lenta. The finding of typical Aschoff's bodies in the myocardium is striking, particularly in view of the much discussed relation between streptococci and rheumatic fever. In this connection I refer also to the articular changes of the fingers which are those of a chronic deforming infectious arthritis. Unless one assumes a combination of sepsis lenta with rheumatic fever, our case can be interpreted as supporting the conception of the streptococcic etiology of rheumatism. Our case also shows that sepsis lenta may lead to the blood picture of aplastic anemia.

The anatomical diagnosis can be summarized as follows: sepsis lenta (*Streptococcus viridans*); chronic tumor of the spleen with small anemic infarct; Aschoff's bodies in the myocardium and slight hypertrophy of the heart; severe impairment of the granulopoiesis and toxic injury to the megakaryocytes; acute glomerulonephritis; nodose goiter; subicterus.

ACUTE STEM CELL LEUKEMIA

DR. TICE: Entered October 6, 1932; died October 30, 1932; examining room diagnosis bacterial endocarditis.

Mr. G. K., a white male, aged twenty-three, stated that the present illness began two months ago and was initiated by the development of a facial paralysis involving the left side and two weeks later appeared on the right side. There was no involvement of the upper or lower extremities until one month ago when the legs became stiff. Five days ago the eyes became "blood shot" and at the same time there developed a discomfort and pain in the maxillary joints when-

Anatomical Diagnosis.—Acute leukemia of hemocytoblastic type with infiltration in the thymus, breasts, epididymi, testicles, spleen, pancreas, adrenal and epicardium; leukemic tumor of spleen and liver; generalized lymphadenopathy; severe anemia; hemorrhages in the conjunctivae, renal pelvis, pelvic fat tissue and underneath the endocardium of the left ventricle; acute emphysema of the lungs.

cardium over the left side of the septum. The weight of the spleen was 495 Gm. and that of the liver was 2240 Gm. Both organs were soft and pale and at their hilus there were groups of enlarged, soft and pale gray lymph nodes. Both kidneys contained many grayish-white nodules from 6 to 15 mm. in diameter. There were hemorrhages in the pelvis of the kidneys and about the urinary bladder. The peripancreatic and periaortic lymph nodes reached a greatest diameter of 70 mm. They were medullary, pale pink-gray with irregular dark red patches.

Both epididymi were thickened and were composed of a firm, homogeneous and whitish tissue which extended for several millimeters into the testicles. The bone marrow was firm, light yellow-gray, mottled with purple-pink.

Microscopically the blood-forming organs were found to be densely infiltrated by round cells from three to five times the size of lymphocytes. The nuclei of these cells were round and finely reticular and were surrounded by a basophilic cytoplasm free from granules. In the bone marrow 61 per cent of the cells were of this type and there were also many very young nucleated red cells (39 per cent) which often appeared very large, while others were small and crippled. Megakaryocytes were scanty. Seven-tenths per cent of the cells were neutrophilic myelocytes and 0.3 per cent were myeloblasts. A few plasma cells completed the picture. In the liver the infiltration occupied chiefly the portobiliary septa, extending often into the peripheral part of the lobules. The spleen contained the lymphoid cells in the pulp and in the follicles and also the trabeculae were infiltrated by these cells. The axillary, tracheobronchial, peribiliary, peripancreatic and periaortic lymph nodes revealed a uniform picture, the lymphoid cells having completely replaced the normal elements. The nodules in the kidney, the thymus, the breasts, the epididymi and the hilus portion of the testicle were composed of the lymphoid cells which often showed mitosis of the nucleus and which were imbedded with a fine reticulum. Infiltration of lymphoid cells was also found around the lymph follicles of the ileum, in the epicardium, in the pancreas and in the medulla of the adrenals.

The type cell in this case is identical with the stem cell from which all the blood cells are derived (hemocytoblast). The hemocytoblast (Ferrata-Maximow) may differentiate into five directions, namely, into myeloblasts, megakaryoblasts, erythrogonias, lymphoblasts, or monoblasts. These five types of cells then mature to granulocytes, megakaryocytes (the source of the blood platelets), erythrocytes, lymphocytes, and monocytes respectively. In acute stem cell leukemia the precursor of all these cells proliferates so rapidly that there is no time for further differentiation.

According to Maximow and others the undifferentiated stem cells are normally present throughout the body. They are a part of the protoplasmatic reticulum of the organs of the reticulo-endothelial system, and they join with histiocytes, pericytes and fibrocytes in forming the adventitial sheaths of the small blood vessels. Normally these cells mature only to histiocytes, fibrocytes and lymphocytes. When stimulated they may differentiate also in the other direction (e. g., in infection). In leukemia they acquire excessive abnormal myelopoietic, lymphocytopoietic or monocytopenoietic potencies or they proliferate without any tendency to differentiation. In this latter instance we speak of hemocytoblast or stem cell leukemia, which always takes an acute course.

probably known for many generations before it was placed in the Talmud as part of the Law. Generations later Dr. Nassé rediscovered these facts and formulated the law of transmission of hemophilia which is known as Nassé's law. This law, briefly stated, is that hemophilia occurs only in males while it is transmitted through the unaffected female; in other words, a hemophiliac's own children are normal, but his daughter's sons may have the disease.

So far as is known the classical writers of ancient civilization made no definite reference to this disease. Even in the Aphorisms of Hippocrates there is no statement that can be ascribed to hemophilia. In the Pharsalid of Lucan, written about the time of Julius Caesar, there is a passage which could refer to this hemorrhagic condition. Albucasis, a Moorish surgeon, about the eleventh century, states that in a certain village there were men who when wounded suffered an uncontrollable hemorrhage which caused death. The same accident happened to the boys if their gums were rubbed harshly and they most commonly died. In 1635 Philip Hachstetter gave a fair but incomplete picture of this disease. He told of a boy who bled from the cord at birth and as he grew older he had severe nosebleeds and bled from the bowel and into the skin. In 1793 George W. Consbuch in the *Medicinishe Ephemeriden* wrote: "On the fourth of November I was called into the country to see an eleven year old boy who two days before had cut his thumb and without being able to stop the flow of blood by any means bled to death before I could reach the spot. A brother of this boy several years before had likewise bled to death from a slight wound. Several brothers of the mother had died in the same way. All of the female sex in the family are so far as I know free from this unfortunate idiosyncrasy." This is an excellent picture of a true hemophiliac family. This article brought forth no comment either from the medical profession or the public.

In 1803 Dr. Otto of Philadelphia published in the *Medical Repository*, "An Account of an Hemorrhagic Disposition Existing in Certain Families." In this article he describes briefly the

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HEMOPHILIA

OUR clinic today is devoted to an interesting, relatively rare disease, hemophilia. This disease, although infrequent, is widespread. It is characterized clinically by excessive hemorrhage which may be spontaneous or may follow injury, even the most trivial. It is almost always hereditary, occurring in males and being transmitted through the females.

The history of this disease is so interesting that it is worthy of a brief review. The earliest reference appears in the Talmud, the ancient holy book of the Hebrews. Here is told the story of four sisters who lived in the city of Zippora. The eldest sister's first son bled to death when he was circumcised. The same fate was meted out to the second sister's son and likewise the third. The fourth sister bore her first son in sorrow for she knew the fate of her sister's sons. She went with her troubles to Rabbi Simon ben Gamaliel, who ordered that her son be not circumcised (Talmud, Tractat, Jebamoth, about 2 A. D.). Likewise in the same Tractat it is written "if a woman has her first baby cut and he dies, and again a second, then shalt she not have the third one cut, and if two children of the same mother or a child of each of two sisters die in succession as a result of circumcision, then it shalt not be performed on the third child." Thus the first definite reference concerning the peculiar hereditary properties of this hemorrhagic disease is in Holy Writ. Here under the subject of dispensation from circumcision, there is quite a detailed description beautifully illustrated by the examples quoted above. These show clearly that the hereditary tendency of this disease and its sex-linked transmission were known to the ancient Hebrew tribes. It was

to external injury. In other instances hemophilia may not be made manifest until the child meets with severe injury. Hemorrhage and hematomas are common at the time of the eruption and loss of the deciduous teeth. In less severe cases the earlier symptoms may be so slight as to be unnoticed until early adolescence, at which time hemarthroses are very common. In one of our patients the characteristic joint hemorrhages did not appear until after the thirty-fifth year and the diagnosis was not established until after the fortieth year. During the interim he was treated for arthritis. Some patients have a tendency to improve after they pass their teens, while others become worse. In one of our families the disease is quite mild until the twelfth year. It then becomes progressively worse and very few of them survive the twentieth year. Some of the apparent improvements in the second and third decades of life are due to the patient's having learned to protect himself from external violence. Because these histories are so similar we will read but three representative ones.

Case I.—W. U., aged eleven, from Massachusetts. This history was written by the child's mother from memory.

1. First noted at circumcision; nine days old; hemorrhaged three days; lost two and one-half pounds.

2. About ten months: Black and blue spots on legs noticed when he began to crawl.

3. At one year: Got severe bump on forehead, bled into eye socket, behind ears, into throat; large swelling on side of face.

4. Twenty-two months: Bit tongue, bled six days in spite of all treatment.

5. Twenty-eight months: Bit tongue again, cauterized. Ten days later scab came off, bled worse than at first. Cautery again lasted four days. Cautery again. Bled again in twenty-four hours. Cautery and thromboplastin injected into back; started to bleed again; clot stayed on tongue.

6. Almost three: Bumped side of cheek against piano bench. Swelled both internally and externally. Teeth held apart for several days by internal swelling. Outside black and blue from eye to throat and even into other eye.

7. Almost five: Elbow joint inflamed and hot after slight bump; suffered several days. At same time fell and hurt hand; suffered a large swelling; recovered.

8. Almost five: Right ankle swelled and was extremely painful with general fever. Five successive attacks with diminishing severity.

9. Five years: Left knee developed swelling and pain, accompanied by general fever which followed simple fall. Got well.

10. Six years: Another attack in left knee.

occurrence of this idiosyncrasy in the male descendants of a woman named Smith who had settled seventy or eighty years before in the vicinity of Plymouth, N. H. Dr. Otto stated: "Males only are afflicted and all are not liable to it; though the females are free, they are capable of transmitting it to their children." Dr. Otto himself had not seen nor treated any of these patients. He received his information from "gentlemen of character" living in the neighborhood of these patients. He also had heard of similarly afflicted families living in New York and Maryland, so the disease was apparently quite widespread even at that early date. The word "bleeder" is used by Otto probably for the first time in medical literature, and with this explanation, "for that is the name given to them." It would appear that this disease was well known even at that time to persons living in the vicinity of those afflicted. This article met with acclaim and brought forth comment from the entire civilized world. In 1813 Dr. Hay reported the famous Appleton-Swain family of Ipswich, Mass. It was in 1820 that Dr. Nassé formulated the law of transmission of hemophilia that bears his name. Schönlein in 1828 first gave to bleeder's disease the name hemophilia. In 1894 Dr. Wright brought out the fact that the clotting time of hemophiliac blood was prolonged. These represent the high lights in the history of hemophilia.

During the last three years we have had the opportunity of studying 55 patients with hemophilia. The histories of all are very similar. They differ only in degree. The very severe ones are recognized early in life, sometimes during the first few days. If they are born into a hemophiliac family the symptoms are looked for. Not rarely infant hemophiliacs bleed from the umbilical cord. This cord bleeding may not occur immediately after birth but may have its onset on the fourth or fifth day of life. The diagnosis of hemophilia is often made following circumcision. In severe cases the imprint of the nurse's fingers will be left on the child's body in the form of subcutaneous hemorrhages. Very often the diagnosis is not made until the child begins to walk, when he is first exposed

He is well developed, well nourished and above the average mentally. The right elbow is somewhat enlarged. It can be extended fully and can be flexed to 65 degrees. No crepitus is present. Finger and wrist joints are normal. The left elbow presents the same condition as the right. The lower extremities show considerable muscular atrophy, especially below the knees. Both knees are enlarged and spindle shaped. There are numerous subcutaneous hemorrhages scattered over both lower extremities. The right knee has marked coarse crepitus. It can be extended to 130 degrees and flexed to 35. The ankles show a high degree of drop foot. The left knee has marked coarse crepitus, can be extended to 170 degrees and flexed to 65. The knee jerks are present. He is able to move his left leg without aid, but the right leg he moves always with his hands (Fig. 65).

Case II.—The next history that we will read is of E. C., aged eleven. This boy is from a definite hemophiliac family. He and his only brother, aged four, are high-grade hemophiliacs. He was a full-term normal baby. At thirteen months he bit his tongue and bled for two days. He had many severe subcutaneous hemorrhages over the entire body. At two years he had a hemorrhage into his spinal column. Since his second year he has had hemorrhage practically every week. Every joint in his body has been involved at some time. He has bled for about a week with the loss of each deciduous tooth. Several transfusions have been performed as life-saving measures. When E. C. was four years of age his mother began to keep a diary of his hemorrhages. This diary occupies 18 pages of 20 lines each and almost every line represents a hemorrhage. Nineteen twenty-seven seems to have been his worst year, for this occupies 8½ pages. We will read 2 or 3 pages of this history for it will give us an idea of the life of a hemophiliac and his parents.

March 11th: Three nosebleeds; right ankle and knee swollen, discolored and painful.

March 14th: Right leg very painful.

March 19th: Right leg still swollen, cannot walk; admitted to Mercy Hospital.

March 21st: Both legs in splints.

March 28th: Right arm swollen.

March 30th: Right arm put in splints.

March 31st: Very sick; swelling on the right side of ribs and back of neck.

April 1st: Gravely ill and does not recognize anyone. Stomach will not retain anything.

April 2nd: Relieved of pain in stomach, but condition is very serious; a blood transfusion being the only means of saving his life, he is given 250 cc. of blood taken from his Uncle Jack because his Daddy could not get there soon enough. Immediately after the blood transfusion he had color in lips, ears and cheeks, and slept well all night.

We will skip from April 2nd to April 16th. During this time he had about ten hemorrhages.

April 16th: Neck swollen; hemorrhage on left side of face; also on inside of mouth and gums. Hemoglobin 42 per cent.

April 17th: Had another blood transfusion of 400 cc.

11. Six years: Had general enteritis which local doctors diagnosed as appendicitis but would not operate. Said death from appendicitis no worse than from hemorrhage. Treated by hot packs, ice, high enemas. Stool contained blood. This attack began with vomiting, general fever, pain in the abdomen; he kept right leg drawn up. At the same time the left knee became painful and swollen. A month later the knee became worse. He was able to walk again. After two weeks at home the same knee suffered a hemorrhage. He then had six days of hematuria.

12. Seven years: Very severe trouble in left knee; also left thigh. Much pain and swelling for two weeks; also hemorrhage into right upper arm. This was in November. He was not able to walk even on crutches until spring. A few days later he had hemorrhages into both ankles. Then the right knee became swollen. He had a succession of attacks in the right knee. Since this time he has never been able to walk except last summer when he tried it with

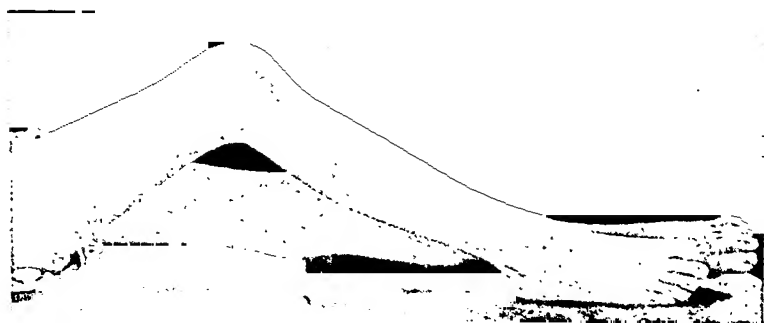


Fig. 65.—Lower extremities of W. U. Observe the inward rotation of the left leg, the flexion of the right knee, the high degree of foot drop and the subcutaneous hemorrhages. The garter level is easily seen on the right leg below the knee; the darkened area represents multiple petechial hemorrhages.

crutches, but two weeks later had a hemorrhage into his knee. He has had numerous hemorrhages into both knees since that time. There were many other attacks, knees, hips, arms, large bruises, and bleeding from the loss of baby teeth which I have not enumerated. There is no history of hemophilia in our family.

Past History.—W. has had whooping cough, measles and scarlet fever, all quite mild attacks.

This child is a sporadic hemophiliac. His family history is known for four generations and it contains no hemophiliacs. There are three other boys in the family, all of whom are normal.

It is interesting to observe in the above history that the diagnosis was made on the ninth day of life and that his first joint hemorrhages occurred during his fourth year. From his fifth year to the present time he has been unable to walk except for very brief periods. The physical examination we will not read in its entirety, because it is absolutely negative except for the extremities.

This very careful chronology of a severe hemophiliac makes very interesting reading throughout.

Physical Examination.—At first glance he looked like a handsome normal boy. Examination of head, chest and abdomen reveals no pathology. The upper extremities show considerable muscular atrophy, especially below the elbow. Both elbows are swollen in a fusiform enlargement. The superficial veins are rather prominent. Movement is greatly reduced, the angle of motion being about 45 degrees. His greatest extension is about 135 degrees, his greatest flexion 90 degrees. His knees are also involved but to a lesser degree (Fig. 66).

Case III.—Our next and last history is of W. C., aged thirty-one. This history was written by the patient.

"Prior to cutting second teeth, hemorrhagic periods are too hazy to recall definitely.

"At the period referred to, there was some laceration of gum tissue upon eruption of nearly all molars, bleeding was profuse and prolonged, though of just what duration I cannot recall.

"The first severe joint hemorrhage I remember incapacitated me for about nine months. I fell and bruised the left knee which swelled to about three times the normal size, accompanied by intense pain and much discoloration. It pained continuously for about two weeks. After absorption, the joint was immobile and pained upon effort to use it. I had to remain in bed about three months and after getting out had to use crutches for six months.

"I have had numerous hemorrhages in both knees since then, with consequent stiffening and enlargement of joints and muscular atrophy.

"Ankles are somewhat stiffened from hemorrhages. Due to a hemorrhage in the left ankle, I was in bed for about two months with swelling, pain, etc., and was compelled to use crutches for several months.

"I have had three major hemorrhages in left hip joint. The first caused some loss of use for about ten weeks. Second and third were more severe, the hemorrhage with swelling and discoloration spreading into the abdominal cavity and genitalia. This clot was about three months in the process of absorption. There was almost complete loss of sensation from hip to ankle for several years. The condition of this leg now is such that in walking I must step in a certain manner or the leg will collapse. Atrophy of thigh is bad with loss of muscular control just above knee which prevents voluntary straightening of leg.

"I have had several hemorrhages from kidneys, though not severe enough to put me in bed. The only pain during these was when blood clots were passing through ureter. The right kidney was involved more frequently.

"I have had so many hemorrhages into the elbow joints within the last ten years that I've lost count. The use of the left elbow is more limited than the right. An injury to the right elbow some years ago caused stiffening of the

April 23rd: Ankle is swollen.

April 27th: Hemorrhage in left shoulder.

April 28th: Third blood transfusion of 350 cc. of blood taken from his father and injected under the left knee.

April 29th: Incision from transfusion still bleeding.

May 1st: Feeling better but very pale. About 8.30 turn for the worse; was cold and hot at times, mostly cold. Pulse 120. Incision still bleeding. Doctor called about 9.30 and dressed bleeding incision. Pain in abdomen, vomited; anointed for death.

And so it goes on for 18 pages.



Fig. 66.—Roentgenograms of E. C.'s elbows. Note the decrease in the articular space, the roughening of the joint surfaces, also areas of rarefaction in the shaft of the bones below the epiphysis which represent interosseous hemorrhages. These were taken in the position of greatest extension.

This mother has also listed her son's absences from school. This is a typical school term:

September: Lost three days.

October: Thirteen.

November: Eight.

December: Two.

January: Seventeen.

February: Nine.

March: Three.

April: Eight.

May: Five. A total of sixty-eight days. This is about 40 per cent of the school days.

or bruise produces bleeding. Hemorrhage reaches zenith within thirty-six hours. Pain starts to subside after sixty to seventy-two hours, sometimes longer. After that fever comes into area affected. There is pain upon attempt to use the part until absorption is just about complete. A good deal of muscular and joint soreness remains for about a week later. Remission occurs after about one, one and a half to two weeks. When I get these spells there is a feeling of extreme fatigue which lasts a full day.

"My schooling was incomplete. Never graduated from elementary school, reached 7A. School week averaged two days out of five. Very seldom able to complete a full week."

The physical examination of this young man shows the pathology to be limited to the extremities. Both elbows are swollen and are markedly limited in motion. The knees are greatly distended and fluctuation is present. Over both knees are many striae just as one sees on the abdomen of a multiparous woman. These were caused, of course, by the great stretching of the skin and subcutaneous tissues at the time of extensive hemorrhages. The accompanying photographs show the extent of this deformity (Fig. 67).

Theories of Causation.—From time to time various theories have been brought forward to explain the cause of hemophilia. Folklore explains it simply as a "mark" due to certain prenatal influence. One woman during the later months of pregnancy watched the slaughtering of a cow, so her son had the bloody mark of hemophilia. Her two succeeding sons also had hemophilia; each was "marked" because the mother saw the older sons bleed while she was carrying the younger.

One of the most ancient theories is probably the cardiac theory. Lancereaux propounded the nerve theory. Still later it was thought to be due to chronic infection. This, like many other diseases, has at times been laid at the door of syphilis and tuberculosis. Endocrine disturbances have been offered as a cause. There is no reason why hemophilia may not coexist with any other disease. One of our patients showed evidence of tuberculosis. One of our milder hemophiliacs had a four plus Wassermann. Two of them showed definite evidence of anterior pituitary hypofunction, Fröhlich's syndrome. The photographs show clearly the infantile genitalia and girdle obesity, also the definite female contour (Fig. 68). The voice had a high-pitched quality. Because of the recent work on the isolation of the sex hormones of the anterior pituitary gland, we decided to treat one of these boys with the extract from that

joint so that it was impossible to straighten or bend it. After months of slow manipulation, some function was regained.

"About three years ago the right shoulder was dislocated and the accompanying hemorrhage was so severe that limited joint action resulted.



Fig. 67.—W. C., aged thirty-one; note the flexion deformity of both knees and both elbows and the outward rotation of the right leg due to deformity of that hip.

"I have had numerous intestinal hemorrhages in the last twelve years. These were diagnosed as gastric ulcer. The bleeding was very severe.

"For the last five or six years I have been keeping check upon myself in regard to hemorrhages. I have noticed that every six to eight weeks there is a sharp rise in coagulation time accompanied by several outbreaks mostly in joints. At these times I am compelled to remain very quiet as the slightest strain

short, some are thin, and some are fat. The first thirty-five hemophiliacs that we saw had a very scant distribution of body hair, but recently two have been added to our group who would bring delight to Darwin's heart. Some are brunettes and some are blondes. It has been said that the practice of circumcision among the Hebrews would preclude its existence in that race. Five of our patients are Hebrews. One Negro boy, who gave a very definite history of bleeding following injury, was brought to us but his blood findings failed to substantiate the diagnosis.

Hemorrhage, of course, is the outstanding clinical finding in hemophilia. This may follow slight injury or may be spontaneous. The hemorrhage following injury may begin at the time of injury or may be delayed for as long as seven to ten days. One little boy whom I remember very well fell on a spiked iron fence forcing the pointed iron between his index and middle fingers, and tearing it out through the palm of the hand at the base of the thumb. This happened on Sunday afternoon. His mother applied a hurried dressing and sent him to the hospital. By the time he arrived all hemorrhage had stopped. Part of the dressing was adherent to the hand by the blood clot. As there was no active hemorrhage that part of the dressing which adhered to the hand was not disturbed. This patient was seen daily for a week and there was no bleeding. The following Sunday he was seated quietly watching a moving picture. He felt something break and then warmth on his hand. When he looked down the entire bandage was blood soaked and he streamed blood all the way to the hospital. In all, thirty stitches were put into the hand. Catgut was used so that it would not be necessary to disturb the wound by removing it. The hand was elevated by suspending it from a frame. Tannic acid was used as a dusting powder. A nurse sat beside his bed and every tiny ooze of blood was sprinkled with tannic acid. He lost a *great deal of blood* but his condition never became critical. He bled freely for five days and oozed at intervals for five more. His hand was kept elevated until it was entirely healed—a period of over three weeks.

We have had many minor superficial cuts and have gotten

gland to see what effect it would have on his hemophilia. First he was given extract of the whole anterior pituitary gland and later the sex hormone of that gland. This patient showed no improvement, if anything his clotting time became somewhat



Fig. 68.—J. H., aged fourteen; observe the girdle obesity, the infantile genitalia and the definite female contour; also the joint deformity of both elbows and the right knee.

longer. His hemorrhages were just as frequent and just as severe as before. Hemophilia still remains an etiologic problem.

Clinical Picture.—There is nothing characteristic about the hemophiliac physically except his joint deformity. There is no hemophiliac facies. Some hemophiliacs are tall, some are

be left in place as long as possible, ten days or more. Here again the object is to keep the patient's blood in contact with the wound until healing is complete. The mold also prevents sucking action of tongue and cheeks and hence the dislodgment of the clot. I have seen hemophiliacs following tooth extraction with their heads so swollen they could not be recognized, eyes swollen shut, hemorrhage into the mouth and tongue, so that the mouth had to be held open and the tongue protruded, the neck and throat so swollen that swallowing was impossible and breathing difficult. These conditions are accompanied by high temperature, 103 and 104 F., and a marked increase in the leukocyte count, 17,000 or 18,000. The return to normal condition requires four or five weeks. If you have ever seen a patient pass through an ordeal like this you will avoid tooth extraction whenever possible.

Besides these external hemorrhages following injury, there are traumatic and spontaneous internal hemorrhages. These may be into the gastro-intestinal tract. The patient may vomit large quantities of blood or have large masses of blood in the stools. One of the most common sites of hemorrhage is from the kidneys. Some hemophiliacs have four or five kidney hemorrhages a year. These last several days to several weeks. The longest we have had lasted eight weeks. The urine is frequently so heavily laden with blood that it forms several inches of clot on the bottom of the container. Considerable pain usually accompanies these, probably due to the passage of clots through the ureters and urethra. Hemorrhages may also occur in the peritoneal cavity where they frequently simulate acute inflammatory conditions. Hemorrhages sometimes occur into the spinal column. In these cases they are not infrequently diagnosed as Pott's disease. One of our boys was kept on a frame for four years with this erroneous diagnosis. Hemorrhages into the muscle and skin are very common. Here they cause swelling, tenderness, discoloration, hardness and local and systemic elevation of temperature.

More rarely hemorrhages may occur into the brain or spinal cord where they cause temporary paralysis. One of our patients

best results by the use of catgut sutures, elevation of the part and keeping it at absolute rest and never disturbing that part of the dressing that adhered to the wound. Tannic acid dusting powder is also a help. The object of all these steps is to keep the patient's blood in contact with the wound until it is clotted. This clot should not be removed but should be allowed to drop off when healing is completed. In short, the treatment is masterful inactivity.

Among the most difficult hemorrhages to control are those from the gums and tongue. Hemorrhages from the loosening or loss of deciduous teeth are best treated by making a mold of soft wood, cork or gutta-percha which fits over the gum and fastens tightly to the teeth on either side of the bleeding point. This mold can be lined with a thin layer of cotton soaked in ovarian extract. These molds have been worn for two weeks or more. During this time the patient is on a liquid diet, with milk, soup, fruit juices, etc. Not infrequently children gain weight on this diet. This same procedure can be followed after extraction of a tooth. Every hemophiliac should retain every tooth that he possibly can because there is grave danger attending extraction. Even with the greatest care severe hemorrhages are apt to occur. Indeed tooth extraction is one of the common causes of death. If the extraction of a tooth is absolutely necessary, then every possible precaution should be taken to safeguard the patient. Most hemophiliacs pass through definite cycles of high and low clotting time of the blood. That phase of the cycle with the lowest clotting time should be chosen for the extraction. This time should be lowered still further by the use of ovarian extract in doses of from 60 to 100 grains daily for at least a week before the extraction. Before the tooth is extracted a mold should be made of the gum and over the tooth to be extracted, and fitted closely over the teeth on either side. The tooth should be very carefully loosened from its socket and lifted out with as little trauma as possible. The socket should not be curetted. The space in the mold that was occupied by the extracted tooth should be filled with cotton soaked in ovarian extract, and the mold applied immediately. This should

heat. The joint should be kept at absolute rest until pain and as much of the swelling as will has subsided, which usually requires a period of weeks. Then diathermy, infra-red, gentle massage and very slow institution of motion. Weight bearing should be begun with great caution. If you are unfortunate enough to see the patient after contracture has begun, it is dangerous and painful to straighten the leg in the acute stage. It is then safest to wait until pain and swelling have disappeared and straighten the leg gradually by the use of casts and turn-buckles. After it is straight, diathermy, gentle massage, etc., can be used.

Blood.—There is nothing characteristic about the cytology of hemophiliac blood. Frequently a secondary anemia is present, the severity of which depends upon the recency and extent of the hemorrhage. The blood platelets are normal morphologically and are present in normal numbers. They are, however, very resistant. The routine blood chemistry, sugar, nonprotein nitrogen, calcium, hydrogen ion concentration, etc., are normal. Fibrin is also normal quantitatively. The most constant and outstanding finding in hemophilia is the great increase in the clotting time of the blood. The length of the clotting time is in direct proportion to the severity of the disease. This is most accurately determined by the test-tube method (Howell's method). By this method most hemophiliacs have a clotting time exceeding one hour. Many of them are five, six, eight hours. Clotting times of eleven and twelve hours are not uncommon. When the blood is drawn from a vein and placed in a tube it looks like normal blood. As it stands the red cell sediment, leaving the straw-colored blood plasma above. The sooner sedimentation begins, the longer the clotting time. The initiation of clotting is dependent upon the rupture of the blood platelets, for when the resistance of hemophiliac platelets is overcome mechanically the blood clots in normal time. Once hemophiliac blood has clotted it retracts normally. If this extruded serum be placed in a separate vessel, it may coagulate again and sometimes even a third time. This phenomenon is rarely seen in normal blood but can be performed repeatedly

had seizures which closely simulated epilepsy. These may have nothing to do with hemophilia, but as they usually occur when he is having hemorrhages elsewhere or is in a bleeding phase, as we call it, they may be due to irritation caused by meningeal hemorrhage.

The most characteristic location for hemorrhage is in the joints. Probably no severe hemophilic escapes crippling due to this cause. On the whole, the more severe the hemophilia the earlier the joint symptoms appear. The joints most commonly involved are the knees, next the elbows, then the hips, ankles and shoulders, then the small joints of the hands and feet. These joint hemorrhages may be spontaneous or may follow an injury. They usually have a sudden onset with great swelling, tenseness, heat and pain. Fluctuation can be demonstrated. There is usually no discoloration as the blood rarely reaches beyond the joint capsule. The joint by preference is held in a position of flexion, for in this position the joint capsule has the greatest capacity. The duration of the symptoms from a joint hemorrhage varies from a few days to many months. After many hemorrhages have occurred in a single joint, there is destruction and ankylosis, with partial or complete immobilization and sometimes subluxation. There is a decrease in the articular space and roughening of the articular surface with osteophyte formation. Crepitus is usually present. After the blood is absorbed these joints closely resemble the arthropathies of chronic inflammatory origin. Muscular atrophy is usually extensive, distal to the involved joints.

The treatment of these joints is very important. If you are fortunate enough to see the patient when the hemorrhage is just beginning before contracture has begun, the application of a posterior splint will prevent a great deal of the deformity, and greatly shorten his invalidism. As to the application of heat and cold, there is much discussion for here we are confronted with physiologic antagonism. Cold contracts the blood vessels but prolongs the clotting time. Heat hastens the clotting time but dilates the blood vessels. We have usually applied cold for the first twenty-four to forty-eight hours followed by

no manifestation of the disease. It seems probable that there is something in the female mechanism that masks the presence of the disease. The greatest difference between males and females is the sex organs and the greatest female sex organ the ovary. In our hands preparations of whole ovary have given the greatest and most prolonged benefit. The dosage has been rather large, the best results obtained when 40 to 120 grains were given daily by mouth or 50 to 200 rat units when given subcutaneously or intramuscularly. The results of treatment are given in considerable detail in the Journal of the American Medical Association.¹

Most of the patients were benefited. Their improvement was both general and specific. The general improvement was shown by an increase in weight and general well-being. The specific improvement was seen by fewer and less severe hemorrhages and a decrease in the clotting time. While most of the patients have improved they are far from symptom-free and much work is yet to be done before this disease is conquered.

¹ November 5, 1932, vol. 99, pp. 1566-1571.

with snake's blood. The bleeding time in hemophilia is usually normal, but in severe bleeding phases it may be greatly prolonged. Capillary resistance as measured by the tourniquet test is usually normal but in severe bleeding phases it may be positive. A study of the capillaries by the use of the capillary microscope shows no departure from the normal. Many statements have been made concerning the increased fragility of the capillaries. In most instances this cannot be demonstrated. At least it seems to play a minor rôle in the mechanism of hemorrhage which is so easily explained by the incoagulability of the blood.

Treatment.—The treatment of hemophilia has been as varied as the theories of causation. Calcium in many forms has been used in large quantities to no avail. Diets of many kinds have been tried, diets high in legumes, diets rich in citrous fruits, high-protein diets, etc. Deficiency in various vitamins has been considered as a cause, especially C and D but A and B have also been blamed, so that diets rich in these vitamins have been suggested. Climate has been considered an important factor and it is undoubtedly true that a warm dry, equable climate is advantageous. Horse serum has been used as a coagulant in active hemorrhage and also as a means of shock therapy after sensitization. It is of unquestionable value in lessening the hemorrhage and shortening the clotting time but is uncomfortable and accompanied by some danger. Therapeutic lights have not proved of value in our hands. Hydrotherapy has been of value as an aid in overcoming joint deformity but of no systemic help. Extract of platelets was used by Kocher and Fonio. Intramuscular blood and whole blood transfusion are of undoubted value. In a severe acute hemorrhage, blood transfusion is the quickest and best treatment. Organ therapy, especially ovary and thyroid, has been used. In our series of cases preparations of whole ovary have given us the best results.

The rationale of ovarian therapy is obvious. Hemophilia occurs only in males and is transmitted through the female. Although the female transmits the disease to her sons she shows

not accentuated and I feel no thrill at the apex. So far as we are able to determine, on physical examination the lungs are negative. He has no history to suggest asthma or asthmatic bronchitis and presents none of the findings of emphysema. Now I shall examine his abdomen. I am able to palpate the edge of the spleen. I find no other masses, areas of tenderness or rigidity. Let us look at the blood picture. The hemoglobin is 115 per cent, and the red blood cells are 5,580,000. We are justified, therefore, in making a diagnosis of polycythemia, but are we justified in stating the type?

STUDENT: No, not without further findings.

You are correct in stating that we cannot yet classify this patient. We must know more about his heart, must observe his reaction to rest, must make sure that we are not dealing with a heart which is showing a decompensation chiefly, let us believe, in the peripheral vascular mechanism. We shall, therefore, fluoroscope his chest and note particularly whether there is anything to suggest pathology. We shall complete the differential of his blood, shall determine the relationship of blood plasma and packed cells, shall attempt to procure a total blood volume reading. However, in spite of the present inadequacy of findings—given a silent polycythemia gradually stealing up on a patient who presents no definite cardiac or pulmonary pathology, who has been at work for many years in the same type of occupation and not exposed to any sort of industrial poisoning, who has definite enlargement of the spleen—our first impression is probably the best, polycythemia rubra. Later observation showed this impression to be correct.

Case II.—Now let us turn to our second patient. He is a much older man who came into the hospital because of a vascular lesion of the right foot with a resulting area of gangrene. What do you notice about this patient?

STUDENT: He is very thin, undernourished, the temporal vessels are tortuous, the face is red, sort of a cherry color and yet cyanotic, the nose is thin, the finer vessels about it are dilated, and this dilatation spreads out onto the face suggesting the butterfly of erysipelas.

That is fine! Will you continue.

SECOND STUDENT: The teeth are bad, there are several missing, there is a marked pyorrhea, the gum margins are soft, spongy and bleed easily and the gums themselves are soggy and red. The palate is very red, especially the soft palate; the tongue is coated and has a cyanotic tint. It looks much like the color of the face. The tongue is moist and the neck is thin.

Now will you carry on?

THIRD STUDENT: The chest and abdomen show this same dusky redness; the hands and lower arms are very red, there is no clubbing of the fingertips, the palmar surface is very red, the arms are long and thin, there is a ring sclerosis of the radial vessels. I find nothing in the heart of significance. The lungs seem to be negative. I cannot palpate the spleen, but to percussion it seems enlarged. The left foot is also dusky and red. When the leg is elevated it does not blanch like a normal leg and foot. When it is allowed to hang down over the edge of the bed there is an accentuation of the color but this is not very marked.

That is very good! Now, what further do you wish to know concerning this patient?

CLINIC OF DR. LE ROY H. SLOAN

COOK COUNTY HOSPITAL

POLYCYTHEMIA: CONSIDERATION OF THE TYPES, SYMPTOMS AND FINDINGS IN POLYCYTHEMIA RUBRA (VERA); PRESENTATION OF PATIENTS

We have several interesting patients to observe this morning. All are suffering from a disease entity which is uncommon but not rare. It is appropriate that in a symposium on anemia we should present that condition which is just the opposite, namely, polycythemia. If we keep in mind the characteristic features of this disease we are surprised at the relative frequency of its appearance and the variety of ways in which it becomes manifest.

Case I.—This patient is thirty-three years of age. Seven years ago he was operated upon for a toxic goiter because of nervousness, palpitation, loss of weight, increased perspiration and easy fatigue. A bilateral subtotal thyroidectomy was done from which he made a smooth recovery. He gained weight, the palpitation disappeared, he returned to work and up until the last two years or so has felt very well. At this time he began to complain again of nervousness and palpitation, which was increased on exertion. A general examination was quite negative except for a thrill which was felt over the apex. No murmurs were found. The basal metabolism was minus 2. No specific treatment seems to have been given for the condition. A second basal metabolism was recorded as minus 17. He was then put upon thyroid extract without relief of his symptoms. During this period his blood pressure remained normal, his urine was normal, he had no particular pain, he had no dyspnea but did have palpitation. On November 7, 1932, he returned for examination, complaining of nervousness, dizziness on stooping over and a general tight feeling. He was having insomnia, sleeping only three to four hours at night. His general feeling is much like that which he had before the thyroidectomy was performed.

As you see him here his appearance is at once arresting. The face is suffused and yet cyanotic. This suffusion is present over the neck, down over the entire chest and abdomen and is particularly noticeable in the dependent hands. The cyanosis is *not* that of one poisoned by coal-tar products or of one suffering from heart trouble. His respiration is quite normal in rate and in amplitude. What does such a picture suggest?

STUDENT: Polycythemia.

That is correct. Now, what more would you like to know about this patient?

STUDENT: The results of examination of his heart and lungs.

Examination of his heart shows it to be slightly enlarged to the left; there is a slightly increased first tone. No murmurs are heard, the second pulmonic is

blood findings; all were males. Patient A, on the service of Drs. George Hall, John Favill and Samuel Plummer at St. Luke's Hospital, was forty-one years of age. He gave a history of periodic attacks of dyspnea, severe throbbing headache, much dizziness, a feeling of fulness across the chest, choking spells when lying down. The headaches were also periodic in character. He was admitted to St. Luke's Hospital because of an acute subarachnoid hemorrhage with facial weakness, weakness of the right arm, aphasia of mixed type, rigidity of the neck. His hemoglobin was variously recorded as plus 100 per cent, on one occasion found to be 157 per cent by the acid hematin method, 130 per cent later. His red blood cell count was 6,780,000 and the white cell count 15,000 plus. He showed all of the typical findings of splenomegalic polycythemia.

Patient B, a private patient, was admitted to the hospital with a massive hemorrhage from a duodenal ulcer and in spite of such a hemorrhage his



Fig. 69.

Fig. 70.

Fig. 69.—Showing the thin nose, the long face, prominent malar bones seen in the majority of patients with polycythemia vera. These patients are usually undernourished, rarely obese.

Fig. 70.—Another view of patient shown in Fig. 69.

hemoglobin was 115 per cent and his red cell count 5,580,000 with a leukocytosis. In addition this patient complained greatly of pruritus. His spleen was enlarged and nothing else was found to account for his condition except polycythemia vera. On closer questioning it was found that he had "had too much blood for quite some time" and had "noticed as a boy that merely shaking his nose started a nosebleed." Our third patient complained purely of mental changes—feeling of apprehension, unsteadiness, lack of logical thought, nervousness, feeling about for words, etc. The physical features of the face and mouth are shown in Figs. 69, 70, and are made from patient A above noted.

I should now like to sketch for you some of the salient points in the diagnosis of polycythemia vera. First let us classify polycythemia into:

STUDENT: The blood count.

The hemoglobin is 120 per cent and the red cell count is 7,600,000. The white cells number 24,000 with 88 per cent polymorphonuclears. We have determined the relative per cent of packed blood cells to plasma and you see there is 53 per cent cells and 47 per cent plasma. This is just about the reverse of the normal figures. While we were about this test we had an opportunity to note the sedimentation rate. At the end of half an hour there was practically no sedimentation in the Wintrobe tube. This was in marked contrast to our findings in a patient with advanced anemia where we found the packed cells as 24 per cent and the plasma as 76 per cent and in thirty minutes there was a rapid sedimentation. Of course, these are not absolute figures for sedimentation but we were interested in the comparison of the two types of blood. I may tell you, however, that in polycythemia rubra the sedimentation is very slow. Now let us dismiss this patient for the present. We will again examine him to rule out tumor of the lung, fibroid, pulmonary tuberculosis, will note carefully the character of the cardiac shadow so as not to miss some pathologic entity which might be responsible for this condition. Here again, however, I feel sure that the patient is suffering from polycythemia rubra vera. Further observation showed this patient to be also suffering from polycythemia vera.

Case III.—At this time I would like to give you the data on a patient who is at Edward Hines Hospital. For these data I am indebted to Dr. Torrey of the staff and those with whom he is associated in the care of this patient.

This patient is a male of forty-one who began to notice recurrent headaches, itching of his fingers, vertigo, insomnia, flushing of the face and dizziness shortly after his discharge from the army. Gradually the symptoms became worse until in 1927 a diagnosis of polycythemia rubra vera was made. The patient would have dizzy spells, becomes sick to his stomach, perspire and noted a numbness first on one side of his face, then in another attack on the other side of his face, perhaps in one arm, the other arm, the whole left side of body, in legs, etc.

His physical examination shows so characteristically the essential findings that I am asking your indulgence to record them here. "The patient is thin, tall, asthenic, undernourished, appears chronically ill. The face is cyanotic, nose, ears, lips very red and with a general flush; the palms are red; heart and lungs are negative. The spleen is palpable one finger below the costal margin. The scrotum is deep scarlet in color. The nails show a tendency to cyanosis, the conjunctivae are hyperemic, the scleral vessels are injected, the retinal vessels are tortuous and distended. There are several large areas of choroidal atrophy indicating old hemorrhage. The throat is hyperemic. There are many missing teeth. The electrocardiogram shows the QRS complex slurred and diphasic in all leads, not greater than 5 mm. with upright T in all leads. This patient in July, 1932, showed a hemoglobin of 182.5 per cent, red blood cells 10,420,000, white blood cells 6200 with predominant polymorphonuclear count. On November 21, 1932, after very successful and skilful treatment with x-ray and phenylhydrazine, the blood was recorded as hemoglobin 84 per cent, red blood cells 4,380,000 and white blood cells 6250. At this time the patient was discharged to await the result of treatment."

Elsewhere¹ I have recorded the histories of three patients together with the

¹ Archives of Neurology and Psychiatry, July, 1933.

mined. The headaches are said to be paroxysmal, to be worse on lying down and associated with throbbing and giddiness. Pruritus is a not uncommon complaint. Paroxysmal dyspnea is present; constipation is the rule, and attacks of abdominal cramps are frequent. Of the neurological symptoms most are referable to the brain as contrasted with pernicious anemia where the spinal cord is chiefly at fault. A colleague relates that one of his patients was frequently accused of "going on a bat." At this time he was not responsible for his actions. He was supposed to be a chronic toper and looked like one. He never touched alcohol in any form. There was complete amnesia for the period of this "bat." It was due to a polycythemia rubra.

Laboratory Findings.—The blood volume is increased two or more times. There is a reversal of plasma packed cell relation. The bleeding time is normal. The sedimentation time is slow. Two of our patients showed normal fragility. One was recorded on one examination as showing beginning hemolysis at 0.44, complete at 0.34, and on another examination beginning at 0.42 and complete at 0.32. The blood pressure has not been significant in any of our patients. The viscosity of the blood is increased. In three of our patients the basal metabolism was within the normal range. It is usually elevated, according to others. The van den Bergh test was negative in three patients until after the treatment was begun. One of our patients had an icterus index from eight to ten. Brown and Giffin have shown the distention in the venous portion of the capillary loop, an engorgement which carries over into the capillary arterial limb. They have shown the increased length of the total capillary loop and have also pointed out that using histamine the rate of flow is from five to ten times as slow as the normal rate of blood flow. The hemoglobin is always above normal, the red cell count averages 7,000,000 in fully developed cases. Usually there is a leukocytosis, though not always. In our patients the predominant cell has shown the polymorphonuclear cell. In two of our patients, myelocytes were found; in one a relatively high eosinophilia. Normoblasts are not uncommon nor are metamyelocytes.

1. **Absolute polycythemia** of which we have (*a*) the erythrocytosis produced by high altitude, congenital heart disease, emphysema, Ayerza's disease; that found in the newborn, etc., a compensatory polycythemia, and (*b*) erythremia or polycythemia vera of Vaquez, Rendu and Widai and Osler.

2. **Relative polycythemia** resulting from severe diarrhea, profuse perspiration, insufficient fluid intake, emotion, asphyxia, hyperventilation, hyperadrenemia, certain drugs and poisons.

3. **Geisböck's polycythemia**, probably one of the above with hypertension.

The etiology of the vera type is not known. No dependable basis has as yet been found, although many have been incriminated. The disease is common in males and between the ages of thirty and sixty. That there is a similar underlying factor in the blood dyscrasias is shown by the cases of pernicious anemia which go over into polycythemia and vice versa, cases of leukemia with terminal polycythemia and vice versa.

The pathology is that of an orderly overstimulation of the erythropoietic and leukopoietic areas. The spleen is always enlarged, though it may not be definitely palpable. The visceral blood vessels are engorged. Arteriosclerosis is common. Cerebral thrombosis, mesenteric thrombosis and peripheral arterial disease are common.

Symptoms.—Elsewhere¹ I have pointed out the great proportion of neurological symptoms in this disease. That this is true might well be inferred from the underlying vascular factor of an overfilled, slowly acting blood flow. The common complaints are headache, vertigo, tinnitus, staggering, sudden transitory unconsciousness, weakness of an arm or leg, thick speech, nervousness, insomnia, scotomata, hemiplegia, hemianopsia, tingling in the hands and feet, loss of memory, choreic manifestations, exhaustion, feeling of tension, lack of concentration, epileptiform seizures, narcolepsy, anxiety neurosis. These symptoms may appear singly or as part of a much larger complex. There is a certain periodicity to the course. There may be a disappearance of symptoms only to recur again. Months and years may intervene before the trouble is deter-

¹ Archives of Neurology and Psychiatry, July, 1933.

the dilated venules, the gingivitis, the fiery palate, spongy gum margins, the dilated and tortuous retinal veins approaching at times the veins seen in the fundi of patients with pulmonary stenosis, the occasional choked disk, the enlarged liver, the enlarged spleen, the dusky red hands and feet which neither blanch normally nor take on much excessive color on change of position, all stealing up on a patient slowly, producing a chronic picture interrupted by more acute signs and symptoms as the disease progresses to end with cerebral hemorrhage, mesenteric disturbance, intercurrent infection, cerebral thrombosis, subarachnoid hemorrhage, etc.

Treatment.—The accepted treatment is with phenylhydrazine hydrochloride. The dosage is variously given as $1\frac{1}{2}$ grains daily up to three times daily. This latter dosage in one of our patients caused so rapid an onset of progressive anemia coupled with hematuria as to become alarming. One might better begin with smaller doses. In one patient the spleen became greatly enlarged under treatment. That the drug is distinctly toxic must be borne in mind. It has seemed that there is apt to be quite a period of nonaction of the drug, then a rather sudden appearance of the anemia once action started. Together with this drug, x-ray therapy over the long bones seems to be of great value. Giffin has followed a large series of patients under control with the use of the above drug. Some of these patients have been able to discontinue the treatment and others have maintained the blood picture on a very small dose.

Acetylphenylhydrazine has been recommended as less toxic than phenylhydrazine. Charles T. Stone, Titus H. Harris and Meyer Bodansky¹ have reported on its use in two cases. Forkner, Scott and Wu² have reported on the use of potassium arsenite in the treatment. More recently the suggestion has come of continuous gastric and duodenal drainage, as also resection of a portion of the stomach or x-ray therapy over the stomach.

¹ Jour. Amer. Med. Assoc., Vol. 101, No. 7, August 12, 1933.

² Arc. Int. Med., 51, April, 1933, p. 616.

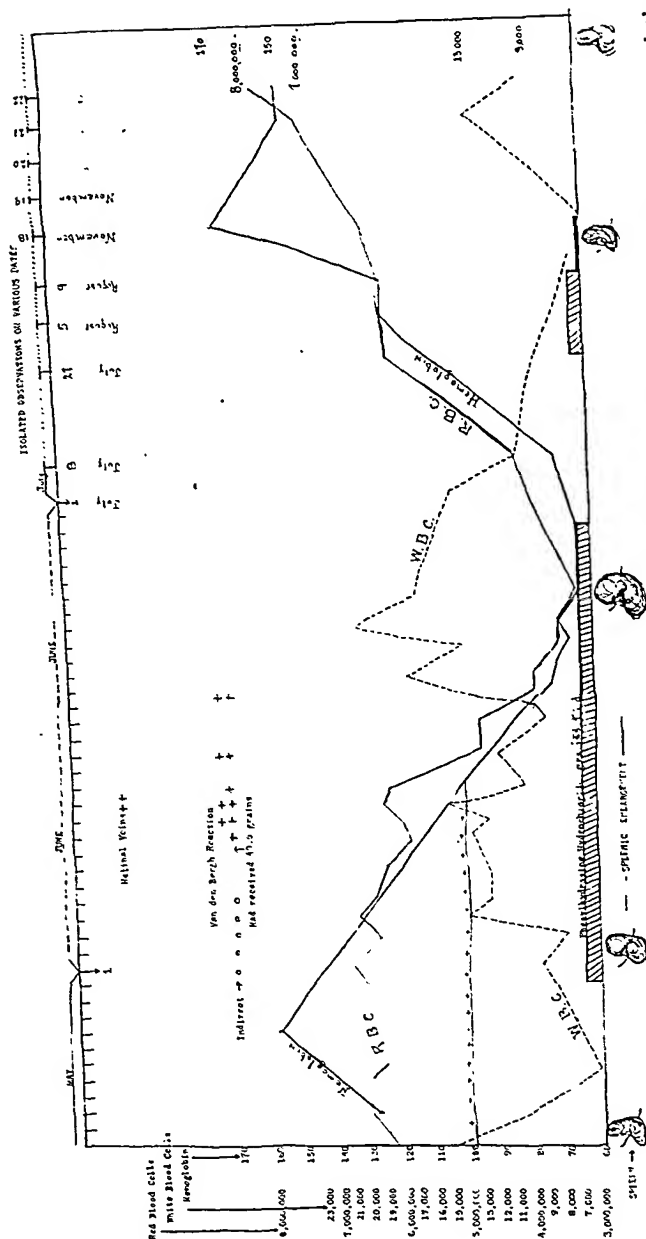


Fig. 71.—Showing the effect of phenylhydrazine hydrochloride upon the red blood count, the white cell count, and the hemoglobin. During the early course of treatment the hemoglobin readings were reported plus 100. Isolated observations during this time showed the hemoglobin to be greatly above this figure. The effect upon the spleen is shown diagrammatically. The rapid elevation of red blood count and particularly of the hemoglobin following cessation of use of phenylhydrazine is well shown.

Physical Findings.—We have noted the typical appearance of the patient—thin, undernourished, asthenic, the cyanotic suffusion, the “buccal suffusion and mucosal lividity” of Osler,

The laboratory findings on admission were the following:

Ewald: Free hydrochloric acid 26 points and total 61 points. No other abnormality.

Stool: Soft, formed; no blood or pus; no parasites; bile present.

Urine: No blood, albumin, sugar or bile pigments in any form were present; no casts found.

Blood Wassermann: Negative.

x-Ray: Chest: Mitral heart configuration and negative lung findings. Stomach: Stomach fills and empties normally.

Blood Count: Hemoglobin 20 per cent, red blood cells 600,000, white blood cells 2100. Platelet count 40,000; coagulation time four minutes. Bleeding time twelve minutes. The differential count: Polymorphonuclears 36 per cent, small lymphocytes 56 per cent, large lymphocytes 16 per cent, monocytes 1 per cent, eosinophils 1 per cent.

Blood smear revealed a moderate variation in shape and size of the red cells. The achromic areas in the red cells were decreased and the color was paler than normal. There were no polychromatophilia or stippling, and no nucleated red cells. The platelets and white blood cells were difficult to locate on the slide. The granulocytes had many lobulations, indicating a shift to the right. There were no evidences on the smear of bone marrow activity.

During his stay in the hospital he developed petechiae, nosebleeds, bleeding gums and a retinal hemorrhage in the left eye. These findings improved after twelve transfusions. He left the hospital after a five-month stay with the following count: Hemoglobin 18 per cent, red blood cells 1,400,000 and white blood cells 4000.

For a month after leaving the hospital he felt comfortable while at rest, but the weakness increased and the epistaxis recurred. He reentered the hospital. The count at this time was hemoglobin 22 per cent, red blood cells 800,000 and white blood cells 3200. No changes were noted in the physical findings or symptoms. He was given two transfusions during his ten-day stay in the hospital and left with the following count: Hemoglobin 31 per cent, red blood cells 1,750,000 and white blood cells 4200.

For the next three months the patient felt somewhat more comfortable and was up and about though he tired very easily. He was very pale and slightly stuporous when he reentered on August 4, 1929. The count on admission was hemoglobin 22 per cent, red blood cells 1,908,000 and white blood cells 4040, which changed following two blood transfusions to hemoglobin 35 per cent, red blood cells 2,400,000 and white blood cells 4200.

Following the last discharge from the hospital the patient noted a marked improvement. He felt stronger, gained in weight and was able to walk better. Four months later he showed a hemoglobin of 35 per cent. He also stated at that time that he had consulted another physician who had sold him an electric belt which he thought was helping him. During this time he was taking liver, iron and arsenic.

The next blood test was done on March 8, 1930, and showed the following: Hemoglobin 70 per cent, red blood cells 3,350,000 and white blood cells 5400. He continued about the same and reported for another count on April 18, 1930. At this time it was as follows: Hemoglobin 65 per cent, red blood cells 2,600,000,

CLINIC OF DR. EVANS W. PERNOKIS

PRESBYTERIAN HOSPITAL

APLASTIC ANEMIA

BEFORE proceeding to a discussion of aplastic anemia I shall first present a typical case history of the disease.

The patient, R. J., aged twenty-three, entered the Presbyterian Hospital on November 12, 1928, on the service of Dr. E. E. Irons. The family history was negative. The past history reveals measles in childhood and typhoid pneumonia at sixteen years. During the five years prior to his present illness he had been employed as a typesetter in a brass factory and was exposed moderately to benzene. He had never noticed petechiae nor any tendency to bruise easily. He had never been jaundiced but had been told that he was sallow.

The present illness began one month before admission to the hospital. His pallor became more marked and weakness developed. The weakness was accompanied by dizziness, buzzing in the ears, blurring of vision and spots before the eyes. These symptoms progressed until the patient fainted at his work and was forced to stop. Palpitation was moderate and with expectoration a slight amount of blood was raised which he felt was coming from the gums. There were no gastro-intestinal nor genito-urinary symptoms and no history of venereal disease. He had no numbness or tingling of the extremities.

The physical examination revealed a well-developed and nourished young man with a marked pallor. The sclerae, gums and mucous membranes of the mouth were very pale. No membranes were noted on the buccal surfaces and no petechiae were seen. The pupils reacted to light and accommodation and no other gross disturbances were noted. The tongue was very pale, not atrophied and had no tremor. The thyroid was not enlarged and there were no palpable cervical lymph glands. The chest was normal regarding contour, resonance and breath sounds. No râles were heard. The heart was slightly enlarged, showing a mitral configuration. At the apex was heard a soft systolic murmur transmitted toward the axilla. A soft diastolic murmur was present at the base. The abdomen was soft and easily palpated. No spleen, liver or kidneys were felt. No inguinal glands or herniae were found. The genitals were normal. Rectal examination showed a normal prostate, good sphincter tone and no hemorrhoids. The prostate was normal in size and consistency. The extremities were normal. The blood pressure was 96/36, the temperature 99.8 F., and the weight 150 pounds.

the lymphocytes, which are formed in the lymph glands and other lymphatic tissues, and the monocytes which, according to the recent extensive work of Aschoff, are developed from the histiocytes of the reticulo-endothelial system.

The bone marrow may be defective in its production of any one of the three cellular elements. When the granulocytes are diminished we have a leukopenia which becomes most marked in the recently described agranulocytic angina. . This condition shows very little deviation in the red cells and platelets. We find the blood platelets characteristically diminished in idiopathic purpura haemorrhagica. The red blood cells may be altered in many conditions without any accompanying change in the white cells or platelets. In the condition which we term aplastic anemia there is defective formation of all three of the cellular blood elements. We thus have diminished red count, diminished white count and fewer blood platelets. There is, however, a variance as to how severely each of the three elements will be involved. With involvement of red-forming tissue the anemia is the striking feature, while decreased number of platelets leads to bleeding tendencies. With marked diminution in the granulocytes there is a tendency to have ulcerations on the mucous surfaces of the mouth and throat. The symptoms will depend on the element involved and the degree of involvement.

The term "aplastic anemia" has many synonyms, the more common of which are: (1) Aleukia haemorrhagica, or primary *myelotoxikose* by Frank; (2) hemolytic aplastic anemia, Turck; there seems to be little evidence for this term as there is no demonstrable hemolysis in this type of anemia; (3) aregenerative anemia, Pappenheim; (4) anemia gravis, Hirshfeld; (5) toxic paralytic anemia, Schneider; (6) hypoplastic anemia, Sheard. Frank has done the more extensive work and his term of aleukia haemorrhagica is coming more into prominence, though Ehrlich's aplastic anemia is still the most common name for the condition.

We distinguish two forms: (1) Essential, or primary, for which there can be no definite etiology ascertained, and (2)

and white blood cells 3600. The patient continued to improve and when he next reported for a count on March 25, 1931, he had the following count: Hemoglobin 81 per cent, red blood cells 4,600,000 and white blood cells 5700. He continued to feel well and did not report until he was asked to come in for a check-up in April, 1932, at which time he showed a decided drop in his blood findings, hemoglobin 40 per cent, red blood cells 2,400,000 and white blood cells 4000. The coagulation time was normal and the bleeding time twenty-four minutes. The patient at this time was pale, weak, and complained of some dizziness. He refused to enter the hospital for a transfusion. He became much worse three months later and entered another hospital in coma, where he died. Permission for an autopsy was refused.

Discussion.—Ehrlich described the first case of aplastic anemia in 1888 in the *Charité Annalen*. It was a very severe anemia following repeated blood loss which showed no evidence of bone marrow regeneration in the peripheral circulation. Since this original description there have been numerous reports and a vast amount of literature has accumulated on the subject. Frank, in 1915, gave the first extensive and comprehensive review. A second report, even more extensive than the first, followed in 1925 by the same author. Eppinger gave an excellent discussion of the condition in his text in 1920.

The present conception of aplastic anemia can be better understood if the function of the bone marrow tissue is kept in mind. It has been shown that the cellular elements of the blood, excepting the lymphocytes and some of the monocytes, are all formed in the bone marrow in adults. Ehrlich was the first to demonstrate that the granulocytes and their precursors, the myelocytes, were formed in the bone marrow, as well as the red cells. He also described a cell which he called the "transitional cell" and which we today call the monocyte and gave its site of formation as the bone marrow. In 1906 Wright advanced his theory that the blood platelets were distinct cellular elements and developed as pseudopods from the large megakaryocytes of the bone marrow. This theory is still the one most accepted, though more recently Schilling has advanced the theory that the platelets were the extruded nuclei of the red cells. We thus have the bone marrow as the active tissue in the production of all the cellular elements of the blood excepting

stances. The pallor is very intense and lacks the lemon-yellow tint so common in pernicious anemia. Petechiae are common on the skin, palate and mucous membranes of the mouth and throat. The spleen and liver are sometimes enlarged. Usually the lymph glands are not palpable.

The laboratory findings are the diagnostic features of the disease. The red cells are diminished in numbers reaching levels below a million in the severe cases. There is no evidence of blood cell destruction as demonstrated by an increased icteric index. The hemoglobin is decreased and the color index is about one. The white count is decreased as are the platelets. The stained blood film shows only slight variation in shape and size of the red cells. There are no signs of regeneration as indicated by the presence of polychromatophilia, basophilic stippling or nucleated red cells. No reticulated erythrocytes are present. When nucleated red cells are present they are of the megaloblastic type indicating a reversion to the embryonic type of blood cell formation. The granulocytes are of the mature type, having many lobed nuclei. The lymphocytes are increased. The platelets are decreased. The coagulation time is normal and the bleeding time is increased. The gastric analysis reveals slight alterations in comparison to the achylia gastrica found in pernicious anemia. The urine shows no abnormal findings. Urobilin and urobilinogen are present only when hemorrhages are present in the skin, tissues or body cavities.

The bone marrow at autopsy shows a fatty or fibrous tissue. Rarely the marrow is red. The diagnosis of the condition is often difficult. When a severe form of anemia exists the possibility of an aplastic form should be kept in mind. Every possible cause of secondary anemia should be kept in mind and excluded. Facts which strengthen the diagnosis of aplastic anemia are an absence of regenerative elements in the peripheral circulation. The increased pigmentation in skin and blood stream speak for a pernicious anemia. The presence of hydrochloric acid and ferments in the gastric contents speaks for an aplastic anemia.

symptomatic aplastic anemia. Some of the more common etiologic factors producing the symptomatic form are: (1) Repeated bone marrow stimulation following frequent blood loss. Everyone is familiar with the fact that too frequent demands on the bone marrow lead to its inability to produce cellular elements. This was the etiology in the first case reported by Ehrlich and in many others since that time. Care must be taken not to term all cases of sluggish bone marrow activity aplastic anemia, as the prognosis varies in the two conditions. (2) Toxic: Benzene, phosphorus, and arsenic are the three most common drugs that are apt to produce an aplasia of the bone marrow. (3) Infectious: Infections of long standing and great severity are often the responsible etiology. The more common are lues, influenza and septicemia. (4) Constitutional: Under this heading may be included senility, climacteric changes and metabolic disturbances as myxedema. (5) Osteosclerosis: This includes tumor metastasis to the bone marrow and multiple myeloma. (6) α -Ray and radium: With the extensive use of both above-mentioned measures in the treatment of so many medical conditions, they are becoming progressively more important as etiologic factors.

The Clinical History of Aplastic Anemia.—The onset is insidious. The younger individuals are more frequently attacked. The symptoms will vary according to the bone marrow element first involved. When the red cells are first involved the symptoms will be those of a severe anemia, pallor, weakness, dyspnea, palpitation and dizziness. Bleeding from the gums, nose, or mucous membranes of the gastro-intestinal tract may follow a diminished number of platelets. Small petechiae are often found. Ulcerated lesions on the mucous membranes of the mouth and throat are frequent with diminished white cells.

An irregular type of temperature is common. Coma and stupor are late manifestations. The most severe cases live only several weeks while milder cases live with remissions for several years.

The physical examination reveals very little in most in-



The treatment of aplastic anemia is very unsatisfactory. When secondary to some other condition the primary cause should be corrected. In the idiopathic form there are few measures which offer any relief. The aim is to stimulate the bone marrow to activity. Liver extract has been tried with little success. The nucleoproteids which have proved so useful in agranulocytic angina have given no relief. Repeated blood transfusions are the present means of treating aplastic anemia. They seem to have a stimulating effect on the bone marrow in addition to increasing the blood volume. The relation of the spleen may prove useful in the future. The spleen has been removed in pernicious anemia with satisfactory results according to some authors. In purpura haemorrhagica removal of the spleen has been satisfactory. In several cases of aplastic anemia removal of the spleen has not been satisfactory but not enough cases are on record to form an opinion. The spleen is removed in the belief that it liberates an endotoxin which affects the bone marrow. All general measures for the treatment of anemia should be used.

fancy do not differ materially from those of the adult. In the crying baby one may observe the retraction of the anterior costal cartilages during deep inspiration. The dome of the diaphragm in the anteroposterior view is higher than in the adult, probably due to the less marked slant of the ribs. In the fetus the diaphragm occupies a higher position than in postnatal life. After the onset of respiration the dome flattens and the level of the diaphragm is lower. This observation has been confirmed by x-ray examinations on newborn children.

Function of the Diaphragm.—Hitzenberger concisely says of the diaphragm that it has three functions. First, it influences respiration; second, it aids in the circulation of the blood, and third, it promotes the function of the intra-abdominal organs. It normally sinks during contraction and increases the lower aperture of the thorax and thus leads to an increase of the intrathoracic space. In this manner the intrathoracic pressure is diminished, and the external air enters the lung. S. Falkenstein maintains that next to the heart the diaphragm is the most important muscle in the body. Nevertheless, paralysis of both sides of the diaphragm induced by severing the phrenic nerves does not seriously interfere with respiration. A unilateral loss of function of the diaphragm may occur without giving rise to subjective symptoms. Thus it is apparent that the diaphragm is not the only muscle of respiration but one of several, and it is no longer to be doubted that respiration may be carried on in some degree without the diaphragm.

Action of Diaphragm on Circulation.—During the inspiratory descent of the diaphragm, as has already been noted, the volume of the intrathoracic space is increased and the pressure diminished. This not only allows the air to enter the lungs but also favors the flow of blood into the thorax. It is readily observed that during inspiration the veins of the neck diminish in size. Though this may not be exclusively due to the descent of the diaphragm, yet it plays an important part. It is certain that during inspiration there is an increase in intra-abdominal pressure.

The diaphragm must not be looked upon only as a suction

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DISORDERS OF THE DIAPHRAGM IN INFANCY AND CHILDHOOD

DURING this hour I wish to review the functions of the diaphragm and its abnormalities under various conditions. It is true that we do not frequently recognize organic defects and deviations from the normal type in this important muscular structure, though perhaps abnormalities in function and structure are of more frequent occurrence than commonly recognized by the clinician.

You will recall from your anatomical studies that the diaphragm is a dome-shaped musculofibrous septum with a central tendon which separates the two great cavities, thorax from the abdomen. The muscular fibers originate from the bony structures of the sternum, ribs and lumbar vertebrae. From these points of origin the fibers of the diaphragm converge, to be inserted into the central tendon. The latter is a thin, strong aponeurosis situated near the center of the muscular vault of the diaphragm, somewhat closer to the front than to the back of the thorax. There are three large openings in the diaphragm to permit the communication of the aorta, esophagus and the vena cava from the thorax to the abdomen. There are smaller apertures to transmit nerves, arteries, veins and lymphatics. It is interesting, from a clinical viewpoint, to recall that the lymphatics of the diaphragm anastomose with those of the peritoneum and those of the pleura which may explain the occurrence of metastatic infections of this region as observed by Poirier and Charpy.

The thoracic duct enters the thorax through the aortic aperture. The muscular attachments of the diaphragm in in-

involved but does not mention whether the diaphragm was studied.

In tuberculosis histologic examination sometimes shows the presence of miliary tubercles in the diaphragm. In the region of the tubercle a parenchymatous degeneration of the muscle tissue may be observed. There is limitation of diaphragmatic motion on the affected side. Tubercles may also occur in the diaphragm during the course of a chronic tuberculosis.



Fig. 72.—Male infant, seven months old. Accidental finding in healthy baby. Hump or cap in center of right diaphragm. The hump attached and moves with diaphragm during respiration.

The excursion of the diaphragm is limited in diaphragmatic pleurisy, subphrenic abscess, diaphragmatic peritonitis, adherent pericardium, and polyserositis or Pick's disease. In diaphragmatic pleurisy adhesions and connective tissue overgrowth limit the mobility of the diaphragm. The connective tissue between the lung and diaphragm may become as hard as cartilage or may become calcified.

pump to produce a vacuum in the thorax which leads the lungs to expand, but it also has an influence on the return flow of blood. This is noticeable by the effect of deep inspiration on the veins of the neck which, though distended, collapse with deep inspiration. An important function of the diaphragm is the forcing of blood out of the liver veins into the vena cava.

It is noteworthy that in the newborn infant the contraction of the diaphragm plays an important function in establishing the systemic circulation. During intra-uterine life circulation in the liver is influenced by the heart's action alone, since the diaphragm is not yet functioning; consequently, on account of the resulting stasis, the liver of the newborn is large. Shortly after birth the liver diminishes in size and this is thought to be due to aspiration of the blood from the hepatic vessels by the functional activity of the diaphragm.

Pathology of Diaphragm.—*Inflammation.*—Inflammatory changes in the diaphragm are for the most part dependent on inflammatory processes elsewhere, particularly in the organs of the abdomen or the thorax. These inflammations are, as a rule, secondary rarely, if ever, primary.

In pneumonia, Hitzengerber describes the changes in the diaphragm as a simple inflammatory process where the muscle structure has lost its homogeneous character with a moderate lymphocytic infiltration, as a result of which there is a limitation of the normal excursions on the affected side.

H. Gideon Wells contributes a paper on "Waxy Degeneration of the Diaphragm." He finds that this condition is usually present in fatal cases of pneumonia. Waxy degeneration is known to appear in muscles which have been excessively stimulated, especially in patients who have suffered from asphyxia. Wells thinks that this form of degeneration may be of great importance in causing respiratory failure in pneumonia, as well as in other diseases requiring severe respiratory effort. Forbus, writing on the same subject, reports 25 cases of fatal bronchopneumonia which were secondary to influenza or measles and which showed waxy degeneration in the rectus abdominis. He states that no other muscles than the recti were

and cause the condition of relaxation, which will be referred to again, or may produce the connective tissue lines described by Chiari.

Actinomycosis of the diaphragm may follow this disease in the mouth cavity or in the lung. In the latter case it is associated with actinomycotic pleurisy or spondylitis. Fistulous tracts may perforate the diaphragm, permitting the passage of the ray fungi from the thoracic into the abdominal cavity.

Syphilis of the diaphragm has been observed in association with syphilis of the liver. The occurrence of gummata in the diaphragm is recorded.

Echinococcus cysts and *Trichina spiralis* infections are the most common parasitic infestations of this muscle. Echinococcus cysts usually originate in the liver. In trichiniasis the diaphragm is frequently involved and may lead to disturbance of function.

Fatty infiltration and degeneration of the diaphragm have been observed in severe anemia and chronic circulatory disturbances. Baldwin Lucke believes that the diaphragm more than any other skeletal muscle is subject to fatty degenerative changes.

It should again be emphasized that inflammatory diseases of the intrathoracic organs as well as inflammatory or degenerative changes of the diaphragm itself inhibit the normal excursions of this muscle band.

Disturbances of Innervation.—Four groups of nerves supply the diaphragm: The phrenic, intercostal, sympathetic, and the vagi.

The phrenic nerve arises from the fourth cervical segment of the spinal cord.

There is no certainty regarding the cerebral localization of the nerve fibers to the diaphragm, though it must be assumed that there are centers in the cerebrum.

Hitzenberger and E. Spiegel performed some experiments on cats and arrived at the general conclusion that the motor centers for the diaphragm lie in close proximity to the motor area of the upper extremity.

A subphrenic abscess may rupture into the abdomen or else externally. Most often it ruptures into the thoracic cavity. If firm adhesions exist between the diaphragm and the pleura, the abscess may perforate directly into the lung. The pleural cavity may become infected without perforation of the diaphragm, the infection occurring through the lymphatic route, not an infrequent occurrence.

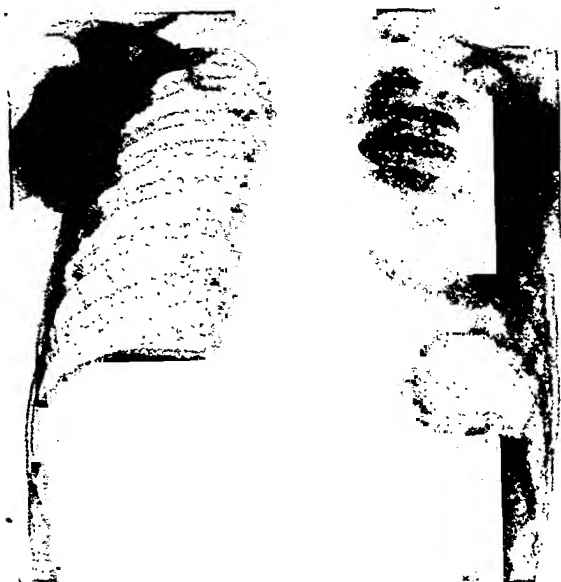


Fig. 73.—Male, four years old. Left pneumonia with an encapsulated pleural effusion. High position of diaphragm. Elevation of left diaphragm due to pneumonia and pleurisy.

Inflammation of the serous membranes, particularly of the pleura and the pericardium, may secondarily involve the diaphragm itself. It has already been pointed out that inflammatory changes of the diaphragm may occur in pneumonia. It has been thought that other diseases, as pointed out by Falkenstein, such as pleurisy, in rare instances osteomyelitis, meningitis or diphtheria, may produce a form of myositis of the diaphragm. These inflammatory foci may lead to formation of scar tissue

produce pain in the shoulder, particularly of the right side, probably due to irritation of the phrenic nerve of that side.

Clinical Manifestations.—If we compare the form and motility of the diaphragm in the adult with that in the infant and child, it becomes apparent that diagnostic deductions concerning the diaphragm are more easily arrived at in adults than in children. In the infant and young child, respiratory movements are characterized by their irregularity. The infant's diaphragm is unequally innervated and paradoxical movements occur readily. The two halves of the diaphragm may not contract synchronously or segments of the diaphragm on the same side may not contract synchronously.

Frequently the central portion of the diaphragm presents a hump which is seen on x-ray examination. It may be present when the diaphragm is at rest or during deep inspiration. Kaestle attempted to associate this symptom with tuberculous bronchial glands, but there is no adequate basis for this assumption.

Movement of the Diaphragm in Disease of the Respiratory Organs.—Marked anomalies in motility of the diaphragm are observed in infiltrating diseases of the lung, as well as in bronchitis of infants and young children. During inspiration the diaphragm makes a strong contraction, but almost instantly makes an upward excursion in order to complete the inspiratory phase. While this type of respiration is usually present in pneumonia, it may occur in other conditions.

In influenzal pneumonia one sometimes observes an infiltration area whose base rests flat on the diaphragm and whose apex approaches the chest wall, forming a triangular shadow with sharp outlines. These processes tend to recede in a brief time. In bronchopneumonia, where physical signs and x-ray examination do not give definite findings, diminished respiratory excursion on the affected side and narrow intercostal spaces will offer valuable aid in arriving at the diagnosis. Incidentally it has been suggested that a displacement of the mediastinal shadow toward the affected side may be utilized as a sign in determining the presence of an otherwise obscure pneumonia.

It has been found that in many instances (about 20 per cent) an accessory phrenic nerve occurs which lies lateral and some distance from the main branch. The presence of this accessory nerve would serve to explain why in some instances after phrenicotomy the motility of the diaphragm continues uninterruptedly. The trunk of the phrenic nerve is supposed to contain not only spinal but sympathetic fibers. Japanese investigators, Shimbo, Aoyagi, and Ken Kures (quoted by Hitzenberger), have studied the sympathetic nerves and Kures has maintained that by cutting the spinal roots, atrophy of the muscle occurred, whereas cutting of the sympathetic fibers led to degeneration of the muscle. According to this, the sympathetic furnishes the trophic fibers. The Japanese performed their experiments on monkeys. Hitzenberger studied the structure of the phrenic nerve in humans and dogs and did not find any nonmedullated sympathetic fibers. Kuntz sums up his consideration of the sympathetic innervation of skeletal muscles by saying, "Most of the experimental data bearing on the relation of the autonomic nervous system to muscle tonus are inconclusive." The phrenic nerve seems to have a sensory centripetal function. After phrenicotomy, irritation of the stump of the nerve produces pain in the shoulder and elevation of blood pressure.

While the phrenic is the main motor nerve to the diaphragm, there are a number of authors who maintain that the sympathetic, intercostals and the vagi supply motor branches also. There is considerable uncertainty and difficulty in proving this latter point. With respect to sensory fibers in the phrenic nerve, Capps and Coleman have shown that by stimulating the central part of the diaphragm, pain in the neck and shoulder resulted. By irritating the anterior and lateral regions, as well as the posterior third, there was pain in the lower portions of the thorax, the regions supplied by the intercostal nerves. These authors also showed that the thoracic portion of the diaphragm is supplied with branches from the phrenic and intercostal nerve. A number of acute diseases in the peritoneal cavity, as well as pneumonia, pleurisy, pulmonary tuberculosis and pericarditis,

due to birth trauma. Cases of this kind have been reported by Dyson, Weigert, Friedman and Chamberlain, Kofferop, J. W. Epstein, and others.

Williams' phenomenon refers to limitation of motion of the diaphragm as a sign of tuberculosis. He believes that limitation in the ascent and descent of the diaphragm occurs on the affected side in apical tuberculosis. This sign has not been dependable for diagnosis in adults and seems to have no greater significance in infants and young children.

Paradoxical movements of the diaphragm are observed in pneumothorax, inflammatory conditions of the muscle itself, or nerve injuries and a variety of other conditions. By paradoxical movement of the diaphragm is meant that the two halves of the diaphragm move in different directions during respiration. During inspiration the affected side of the diaphragm becomes elevated and during expiration it descends, just the reverse of what occurs under normal conditions, while the opposite half of the diaphragm makes normal excursions. The movements may be described as a seesaw motion. This sign is of no value in infants and young children because there is no regular type of motion in the infant's diaphragm. In older children, however, paradoxical movements occur and are of the same diagnostic significance as they would be in adults. Incoordinated movements of the diaphragm have been observed in chorea, the two halves not acting in unison and resembling the movements observed in the paradoxical type.

Hitzenberger, in discussing the influence of pneumothorax or hydropneumothorax on the movements of the diaphragm, says that there are numerous and contradictory opinions expressed, though he believes that a variety of changes in excursion may be present in the diaphragm due to pneumothorax. It may make normal movements; it may remain stationary or it may make paradoxical movements. It is possible that one part of the diaphragm may make normal movements and another portion of the same side may show paradoxical movements. The opinion is expressed that the diminution of intra-

Descent of the diaphragm occurs in severe capillary bronchitis during infancy. Also in emphysema, bronchial asthma, miliary tuberculosis, pleurisy with effusion and pneumothorax. Disease of the pleura may diminish the movement of the diaphragm. Pleurisy with effusion, even if the amount is small, may produce marked interference with the usual mobility of the diaphragm. Empyema may cause a complete cessation of movement. The accumulation of air in the pleural cavity may interfere with respiratory movements.

In pleuritic effusion of considerable extent the intercostal spaces are widened and the ribs and intercostal muscles participate only slightly or not at all in respiration. The diaphragm on the affected side assumes a low position and shows slight or absent respiratory excursions.

Acute dry pleurisy may also cause a diminution in the excursions of the diaphragm because of pain. In the healing of either dry or exudative pleurisy there may be a notching or angulation of the diaphragm due to pleural adhesions. Fibrin masses on the surface of the diaphragm may contract to scar tissue and limit mobility, though it is noteworthy that many of the postpleuritic processes in the young child tend to heal with a complete return to normal. And in a general way it may be said that pleural adhesions in infants and young children are not always of such serious import as they may be in later life.

Overdistention of the lung interferes with the motility of the diaphragm. During miliary tuberculosis the muscular movement may cease entirely. In bronchial asthma there is a cessation of diaphragmatic movement during the inspiratory phase; while during expiration short, irregular movements occur. If a bronchus is obstructed, the excursion of the diaphragm on the same side is diminished or limited. In bronchostenosis the diaphragm may ascend and occupy a high position in the thorax. The position of the diaphragm is high in diphtheritic paralysis; elevation is also caused by pressure of tumors and tuberculous glands, or as a result of birth trauma.

In the literature there are recorded a number of cases of injury of the phrenic nerve causing paralysis, which are usually

muscles is frequently associated. If the two conditions occur in combination, death is liable to result.

In paralysis of the diaphragm dyspnea becomes marked, respiration is of the thoracic type and the accessory muscles of respiration are brought prominently into action. The breathing of a child suffering from diaphragmatic paralysis is typical and easily recognized. In this type of breathing the abdomen is not pushed forward as it is under normal conditions, but is markedly retracted with each inspiration. The character of the breathing should be noted when the child is quiet, because in crying and restless children the breathing may be thoracic in nature.

Duchenne, a French neurologist (1806–1875), first called attention to paralysis of the phrenic nerve in progressive spinal muscular atrophy. Though inhibition of movements of the diaphragm is not frequently described in this condition, I recently saw a boy, thirteen years of age, with a progressive neuromuscular atrophy who suffered from respiratory embarrassment. On forced inspiration the intercostal as well as the abdominal muscles made visible contractions. Fluoroscopic examination showed that the right diaphragm made feeble excursions, that it stood considerably higher than the left half, that it was more than usually flat and that the normal, dome-shaped appearance was absent.

Infundibular or Funnel Chest.—An attempt has been made recently to explain the cause of infundibular or funnel chest by pointing out that the suspensory ligaments of the diaphragm attach the central tendon with the vertebrae on the one hand, together with the anterior muscle bundle, to the lower portion of the sternum. In this way the diaphragm becomes firmly attached. In some instances this connecting band becomes shortened and consequently there is firm traction on the sternum, causing it to be retracted. It is possible to conceive that this shortening of muscular attachment is a congenital and not an acquired condition, though we so frequently see an infant remaining normal for several months and acquiring the funnel chest as late as the sixth month (Lauenstein).

thoracic pressure or anatomical damage to the diaphragm may cause paradoxical movement in pneumothorax.

One must not lose sight of the fact that increased intra-abdominal pressure from any cause may elevate the diaphragm or interfere with its normal excursions, especially if the muscle itself be diseased.

There has been considerable discussion as to the effect of a pathological change of the diaphragm on its motility. H. Eppinger maintained that the diaphragm of a patient suffering from emphysema, even on naked-eye examination, shows hypertrophy. H. Fromme weighed the diaphragm of men and women in health and found a considerable variation depending upon the size and the development of the individual, though in chronic pulmonary emphysema she always found a diminution in the weight of the diaphragm which would indicate that this muscle is not hypertrophic. Histologic examination has shown definitely that in these cases atrophic conditions occur, but that they are not the only pathologic change to be noted. In association there are inflammatory and degenerative changes with cellular infiltration and areas of necrosis. The connective tissue is markedly increased and the elastic fibers are abundant. These degenerative and inflammatory changes in the diaphragm are sufficient to materially limit the mobility of this muscle. The increase of the elastic substance shows that the muscle of the diaphragm is more or less replaced by scar tissue which acts as a support but lacks motility and contractility.

A high position of the diaphragm may be produced by abdominal distention, due to meteorism, ascites, abdominal tumors or subphrenic abscess. The pressure from below causing elevation of the diaphragm may push the heart upward and to the right. An overdistended stomach may cause the diaphragm to ascend to a considerable degree and may interfere with respiration as well as circulation.

In poliomyelitis the phrenic nerve is not infrequently involved, though as a rule the diaphragm is one of the last muscles to be involved. Paralysis of the diaphragm and intercostal

Spasms of the Diaphragm.—Spasms of the diaphragm may be tonic or clonic. The clonic spasm is of frequent occurrence and manifests itself most familiarly as hiccup or singultus. α -Ray examination shows that a patient with hiccup makes short inspiratory movements and a prolonged expiration. While hiccup occurs occasionally in normal children, it may be of graver pathologic significance. The spasm may have its origin in the central nervous system, which is shown by the fact that it occurs in organic diseases, such as encephalitis, meningitis, hemorrhage or in uremia. It is also observed in cases of poisoning, such as alcohol and nicotine, and in severe infections of the abdominal viscera, particularly in peritonitis and dysentery. It may be due to direct irritation of the phrenic nerve as in pericarditis, pleurisy, pneumonia and mediastinitis.

Clonic spasms of the diaphragm have been produced by fracture of the xiphoid process. Such a case was described by Clarence A. Bird. This case is unique in that a clonic spasm resulted from fracture of the xiphoid process. This was probably caused by forcible holding of a retractor by an assistant during abdominal section. The spasm was most likely due to pressure of the fractured bone on the phrenic nerve.

The tonic spasms are of less frequent occurrence. In these cases the epigastrium is protruded, the diaphragm is stationary, the respiratory excursions are diminished. The patient suffers from dyspnea and pain at the sites where the diaphragm is inserted. Spasm may occur in tetanus and has also been described by Lederer as occurring in bronchotetany. It has been observed in tic and chorea. In epileptic convulsions the diaphragm may show rapid convulsive contractions.

Relation of Heart and Circulation to Diaphragm.—As has already been pointed out, in the newborn and young infant the diaphragm is elevated and the dome is flat. According to Hecht, this position of the diaphragm causes the heart to lie in transverse position and close to the anterior thoracic wall. In the roentgenogram the heart occupies considerable space within the thorax. In the newborn and young infant the large part



Fig. 74.



Fig. 75.

young adults may suffer from subphrenic abscess. H. L. Barnard reports 76 cases of this disease and from birth to ten years there were 6 cases and from ten to twenty years there were 5 cases. The greatest number occurred between twenty and thirty years, during which time there were 29 cases. Gatewood, writing on subphrenic abscess, reports 41 cases occurring in the Presbyterian Hospital of Chicago during the previous ten years.



Fig. 76.—Subphrenic abscess in female child, aged seventeen months. Air bubble and fluid collection below diaphragm. Effusion into right thoracic cavity. Child operated upon. Recovered. (Courtesy of Dr. Joseph Brenne-
mann, Children's Memorial Hospital, Chicago.)

Among these were two male children aged fifteen and eight years, respectively. John H. Jopson collected 68 cases from the literature since 1893. He quotes Maydl who collected 179 cases of this disease. In this series only 10, or 5.9 per cent, were under fifteen years of age; while in Jopson's series 12, or 17.6 per cent, were in children under fifteen years of age. Jopson shows that subphrenic abscesses are frequently secondary to appendicitis, though infectious conditions of the lung, pneu-

of the heart lies to the right of the thorax. If the diaphragm lies high, the heart is pushed still more to the right.

As the result of pericarditis, adhesions may occur between the pericardium and diaphragm as well as the pleura. Adhesions to the diaphragm interfere with its normal excursion, particularly a descent of its left half during inspiration. If the pericardium adheres to the anterior thoracic wall the heart shadow does not descend with the diaphragm as in normal conditions, but ascends with the ribs. One of the most serious after-effects of empyema in the child is involvement of the pleura in the proximity of the pericardium which produces displacement of the heart in association with fixation of the diaphragm.

In heart diseases changes are observed in the diaphragm. They are similar to those already described in emphysema, and are degenerative and inflammatory in character.

Pulsating movements of the diaphragm in association with tricuspid insufficiency have been studied by Hitzenger. This movement appears only in the anterior half of the diaphragm and consists of a gradual excursion with a jerky rise and fall. This venous hepatic pulsation becomes more distinct if the patient holds his breath, even if for only a short time. In cases of tricuspid insufficiency one observes on the right side of the diaphragm a systolic elevation and a diastolic descent as an expression of a positive hepatic venous pulse. Anomalies in the position of the diaphragm do not change its pulsation, but obliteration of the pleural spaces and fixation of the diaphragm by adhesions interfere with pulsatory movements.

Subdiaphragmatic Abscess.—A review of the literature indicates that subphrenic abscess is infrequent in young life. A. Czerny is quoted as having said that he never saw a well-authenticated case in all his practice. It has been suggested that the large size of the child's liver tends to distend the dome of the diaphragm and fill it more completely than it does in adults, and by this decrease in spatial relationship, a certain protection is afforded against abscess formation. Nevertheless, a statistical study of reported cases shows that children and

with a subdiaphragmatic abscess. Occasionally one or more gas bubbles are observed in the accumulated purulent effusion. At times it may be difficult to demonstrate the subdiaphragmatic purulent exudate by the x -ray examination. Repeated examinations are sometimes required to show the presence of subphrenic abscess.

The diagnosis may be confused with paranephritis, liver abscess and at times a pleural empyema with or without pneumothorax. While the roentgen examination may at times fail to reveal the abscess on the first examination, nevertheless its employment for diagnostic purposes is invaluable. Fluoroscopy presents definite advantages over the usual film examination. Films made in the upright position often aid in the x -ray diagnosis. The presence of a fluid line below the diaphragm is of great value in diagnosis, but unfortunately it is not always present. It may be necessary to introduce an aspirating needle to confirm the diagnosis. This should be done with extreme caution and with surgical preparation so that immediate incision and drainage may follow exploratory puncture because it is obvious that if the pleura is not already infected, it is almost sure to become so by withdrawing an infected needle from the subdiaphragmatic space into the thoracic cavity.

Relaxation or Eventration.—Relaxation or eventration is recognized by the high position of the diaphragm. This condition occurs nearly always on the left side. It is scarcely ever observed on the right side. Bayne-Jones and Eppinger have reported cases of relaxation on the right side. In cases of relaxation, the abdominal organs are pushed up with the diaphragm before them so that they appear to lie in the thoracic cavity. In extreme cases the dome may reach the second anterior intercostal space. In the same patient the relaxation may be present at times and absent at other times. Assmann describes one in whom the relaxation was not present in the erect position but was apparent in the recumbent position. In these cases the diaphragm does not present the configuration of the normal curvature but one sees several arches. These may be parallel or they may cross each other.

monia and purulent pleurisy are also etiologic factors. Descending infection through the diaphragm may occur, but not with great frequency.

Maydl refers to 10 patients of fourteen years and less and gives the following causes for the existence of subphrenic abscess. Three were due to subcutaneous traumatism, 2 to cholecystitis, one during and the other following typhoid fever, both associated with rupture of the gallbladder. One was due to a perforated gastric ulcer, 1 to perforation of the transverse colon, 1 to caries of the three lower ribs and 1 following right-sided pleurisy and pneumonia. Among other causes mentioned by Jopson comprising a study of 12 cases, 6 followed appendicitis, 1 duodenal ulcer, 1 caries of the dorsal vertebrae, 1 after traumatism and 1 after calculous cholecystitis. Jopson reports a young infant, fifteen months of age, who showed a soft fluctuating swelling about the size of a small fist in the axillary line. The abscess was opened and it was found that the cavity was on the upper convex surface of the liver. The interesting point about this case is the age of the child. Fifteen months is among the youngest of the reported cases. In Maydl's series twenty-six months was the age of the youngest child. Baginsky reported a child two and a half years of age who developed subphrenic abscess secondary to appendicitis.

The most frequent source for subphrenic abscess is a suppurative process in the abdominal cavity, particularly acute appendicitis. Abscess of the liver, cholecystitis, abscess of the spleen or pancreas, rupture of a gastric or duodenal ulcer may cause subphrenic abscess. The diaphragm is pushed upward in this condition and its motility markedly interfered with.

As in adults so in children, subphrenic abscess usually occurs on the right side, though it may be localized under the left diaphragm. As has already been noted, the movements of the diaphragm are decreased or they may remain stationary. Paradoxical movements are sometimes observed. It has been thought that the disturbances in motility were due to a paralysis of the diaphragm in consequence of inflammatory changes in that muscle. An associated pleural exudate frequently coexists

sis is the differentiation of relaxation from diaphragmatic hernia. The two conditions may resemble one another so as to make the diagnosis confusing. Several authors maintain that in relaxation the diaphragm makes simultaneous movements with respiration, whereas in hernia the excursion of the outline of the diaphragm makes paradoxical movements but even this differentiation is not valid because the excursions in hernia may be similar to those in relaxation, especially if there are adhesions in the former instance. Others have pointed out that if upon repeated examination the contour of the diaphragm remains unchanged, the condition of relaxation may be assumed, whereas if the contour changes from time to time, hernia is more probable.

It is important for diagnosis if the outlines of the stomach and the shadows of the diaphragm can be separated so that it can be shown that the stomach lies under the diaphragm. This may be facilitated by permitting the gas to escape, diminishing the size of the gastric air bubble. In this way the stomach recedes from the diaphragm and the two shadows may be definitely separated. The ingestion of barium after the escape of gas will assist materially in bringing the stomach and diaphragmatic shadows into better differentiation. Relaxation of the diaphragm shows in x-ray examination not infrequently the evidence of extreme or total paralysis. It is evident that relaxation of the diaphragm may present difficulties in differentiation from both hernia and paralysis; that it may fail to be recognized clinically and that the most careful and expert roentgenological examination may fail to establish the precise nature of the affection.

Pathologic Anatomy.—The pleura, the central tendon and the peritoneum are usually intact. On the affected side the muscular portion of the diaphragm may consist of firm tendon-like connective tissue interspersed here and there with muscle fibers. In another group the muscle structures are present but are infiltrated with fat or, indeed, may progress to fatty and hyaline degeneration.

A defect in the structure of the phrenic nerves has been con-

It should be stated that owing to the anomalous position of the diaphragm the abdominal organs are pushed up and seem to lie in the thoracic cavity. This fact makes the differential diagnosis between diaphragmatic hernia and relaxation of the diaphragm difficult. Not only is this differentiation difficult, but also the fact that dulness and diminished breathing are elicited where normally respiratory sounds are heard suggests the pos-



Fig. 77.—Relaxation or eventration with dextrocardia in boy aged ten years. Left diaphragm definitely elevated. Heart displaced to right. (From Gralka, Roentgendiagnostik.)

sibility of pleurisy with effusion. Other conditions, such as paralysis of the phrenic nerve, pneumothorax and pyopneumothorax, may be mistaken for relaxation of the diaphragm. In most of these cases the heart is pushed considerably to the right and the heart tones are heard to the right of the normal location. The esophagus is also bent, curved or pushed to the right.

Roentgen Examination.—The greatest difficulty of diagno-

gastro-intestinal symptoms. At times they complain of pain in the left thoracic region, others complain of moderate dyspnea, possibly due to the displacement of the heart. Another small group suffers from an associated bronchitis with cough and expectoration. Gastro-intestinal symptoms occur, such as pain and fulness after eating.

Symptoms are referred to the heart, stomach, intestine or lungs. They manifest themselves in the form of sticking pains, difficulty in breathing, pressure symptoms and palpitation. Dysphagia is frequently present and depends on a change in position of the esophagus produced by pressure. As a rule, such patients have no difficulty in swallowing fluid though they do swallow large, hard morsels of food more easily than small ones. In severe cases the patients show an anxious expression, respirations are increased, and dilatation of the alae nasi is frequently observed.

Physical Findings.—Percussion reveals zones of tympanitic areas associated with dulness in the upper portions of the chest. These findings vary with change of position. Tympany indicates gas, and dulness indicates fluid in the stomach. The dulness elicited has sometimes given rise to the diagnosis of pleurisy. One should avoid inserting a needle in such patients on account of the danger of peritonitis.

Auscultation reveals diminished breathing, though one sometimes hears sounds due to intestinal gas. The important point is to differentiate relaxation from diaphragmatic hernia. A carefully elicited history is of value to an experienced clinician in making this differentiation.

The Diaphragm in the Asthenic Type of Constitution.
—The diaphragm in the asthenic type of constitution is discussed by Karl Hitzenger. He observes that the asthenic type of child is usually recognized as one who is tall but particularly thin and who has a narrow chest. The neck is usually long, the shoulders steep and sloping, the chest is flat, the costal angle slopes more than normal. The posture of these patients is usually bad. The lungs are voluminous and the heart is small. The heart and the vessels are inclined to be underdeveloped.

sidered a possible cause of the relaxation. In one instance adhesion of the left phrenic nerve to the pericardium was supposed to have caused pressure necrosis of the nerve. Diminution in the size of the nerve fibers and atrophy of the left phrenic nerve have been observed in eventration.

The neighboring organs may be affected. The right lung is not involved, though the left is diminished in size. Occasionally emphysema, atelectasis and pigmentation are observed. Several theories have been advanced as to the cause of this condition, among which may be mentioned differences in pressure on the two halves of the diaphragm, or a disease of the muscle causing weakening and thinning, or atrophy or pressure on the phrenic nerve causing defective innervation.

The condition may be congenital in origin. Many who have closely studied this affection are of that opinion. The condition has been observed in fetuses and newborn infants, and it has not infrequently been found to be associated with other congenital anomalies, such as three lobes in the left lung, an open foramen ovale and congenital herniae. Extreme diaphragmatic relaxation in the newborn causes respiratory and circulatory difficulties and frequently leads to the death of the infant. After the first year of life the condition is rarely a cause of death.

Alfred Weil reports that up to 1908 only 11 cases of this condition had been recorded in the literature, though he says that in ten years preceding 1925 he has seen it himself twenty times on fluoroscopical examination. Weil advances the opinion, after study of several cases, that the relaxation of the diaphragm may be caused by continuous presence of gas in the stomach or even in the large intestine. In support of this view he believes that the left side of the diaphragm is more exposed to pressure from gaseous distention of the bowel than the right side.

Symptomatology.—Relaxation or eventration occurs most commonly between the twentieth and fiftieth years. Many of these patients may present no symptoms, though some have mild, indefinite manifestations and others have thoracic or

cases only 15 were recognized during life. Greenwald and Steiner report 81 children under ten years of age, of whom 25 were recognized during life. Lauenstein writes on the symptomatology and diagnosis of diaphragmatic hernia in children and gives a bibliography of the recent literature. Carl A. Hedblom contributed a paper on the study of 378 cases in which operation was performed; 19 of these were from the Mayo Clinic and 359 from the literature. According to Hedblom, in a group of cases from the Mayo Clinic which were operated upon, he reported only 2 children, five and nine years respec-

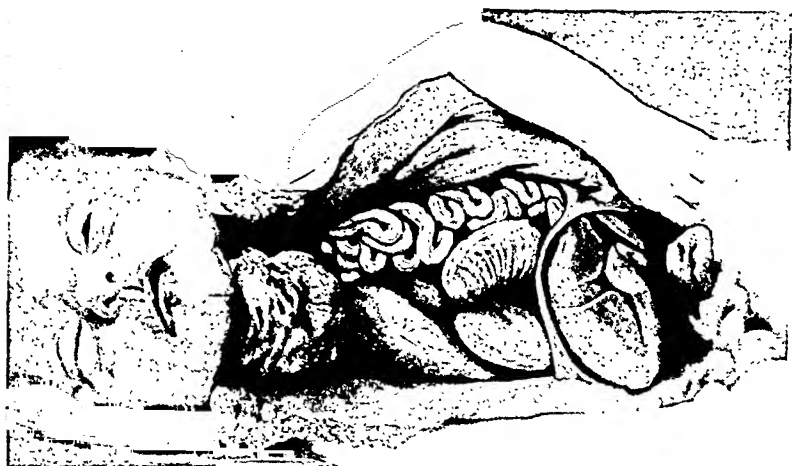


Fig. 78.—Drawing of diaphragmatic hernia.

tively. In the series of collected cases there were 22 children included who were ten years of age or under. A relatively large proportion of the cases of congenital origin reached adult life. Infants born with large congenital hernia, as a rule, do not survive long after birth.

Hedblom's table showing age incidence and etiologic classification of cases of diaphragmatic hernia is given on page 409.

Types.—Two forms of diaphragmatic hernia are usually considered, the traumatic and nontraumatic. The traumatic form is extremely rare in children, though a few such cases have been reported and are due to direct violence, especially

Wenckebach discusses the asthenic thorax and maintains that, owing to the low position of the diaphragm, the swing for the heart's action and its lateral movements are interfered with. In addition to the effect on circulation, respiration is also involved in the low position of the diaphragm. During inspiration the lower portion of the thorax, instead of widening, becomes narrower in the asthenic type of chest. If this condition of the diaphragm occurs in young life while the bony structures of the thorax are still yielding, it has been observed that the upper portion of the thorax takes on increased work, while the lower portion remains relatively inactive. Consequently the upper portion of the thorax increases in size and the so-called "thorax pyriformis" develops.

The diaphragm sometimes participates in the thoracic anomalies produced by asthenic constitution. It has already been indicated that a low diaphragm is an associated condition of the asthenic thorax. The diaphragm is usually flattened, the costophrenic angle is wider and approximates a right angle. By lateral fluoroscopy it is observed that the slope toward the spine is diminished. The diaphragm in these cases, instead of being on a level with the ninth to tenth ribs, is found on a level with the ninth or tenth intercostal space, even as low as the eleventh. The movements of the diaphragm become less frequent. During quiet breathing the movements have ceased or are small. On deep breathing the movements of the diaphragm may be normal or nearly so. A low position of the diaphragm occurring in individuals of asthenic constitution is not indicative of a diseased condition. It simply represents the architectural type of the given individual. On the other hand, a low position of the diaphragm which occurs during emaciation or emphysema is obviously due to definite disease processes.

Diaphragmatic Hernia. — *Incidence.* — Diaphragmatic hernia has received much attention in the recent literature. Greenwald and Steiner have presented an excellent review of its incidence in children since 1912. Previous to their reports Giffin collected 650 cases. Of this group only 6 cases were observed in children under five years of age. Out of his entire 650

opening to a more extensive defect; half or more of the diaphragm may be entirely absent. Herniation may occur (1) through the esophageal opening; (2) through the foramen of Morgagni or Larry's space, and (3) through the foramen of Bochdelaki.

The foramen of Morgagni is found at the junction of the sternal and costal portions of the diaphragm and is really a gap in the musculature which is covered by pleura and peritoneum. The foramen of Bochdelaki is also a gap in the musculature covered by pleura and peritoneum and is found posteriorly at the junction of the lumbar and costal portions of the diaphragm. There is considerable discrepancy in the literature as to the frequency of herniation into the esophageal opening. Aschoff thinks that the herniation through the esophageal opening is of less frequent occurrence than through other gaps. It seems that herniation through the aortic opening is rare and there appear to be no cases reported in the literature where hernia occurred through this hiatus. Greenwald and Steiner remarked on this point that this may be explained by the fact that the aortic opening is anatomically and developmentally not in the diaphragm but behind it. Small herniae of the diaphragm, especially periesophageal, are much more common than is usually supposed.

Hernial Contents.—The omentum is the first of the abdominal structures to enter the thoracic cavity in case of herniation. In order of frequency the organs which prolapse into the thoracic cavity are stomach, colon, small intestine, spleen, liver, pancreas and kidney. It has been thought that the omentum, being the most movable of the abdominal contents, enters the thorax first through suction from the negative pressure in the thorax and drags other abdominal organs after.

Associated Malformations.—Congenital diaphragmatic herniae, as well as some of the acquired forms in childhood, may be considered the result of congenital malformations. Multiple congenital malformations are known to occur and Eppinger has noted that supernumerary fingers and webbed fingers, supernumerary lobes of the lungs, pulmonary atelectasis, horse-

Age.	Traumatic.	Congenital.	Acquired.	Indeterminate.	Total.
Under 1 year.....	2	3	0	1	6
1 to 5 years.....	4	3	0	0	7
6 to 10 years.....	5	2	2	0	9
11 to 20 years....	13	12	1	4	30

where children have been injured by moving vehicles. Some of the children thus injured have been cured by operative procedures. Cases of this nature are reported by Truesdale, Gordon, and others. Empyema and subphrenic abscess may cause inflammation of the diaphragm, weakening its muscular structure, culminating in herniation through the normal openings. There are a few such cases recorded in the literature.

There is considerable discussion as to whether diaphragmatic hernia in childhood is congenital or acquired in the non-traumatic cases. It has already been noted that infants may be born with absence of a part of the diaphragm or with a defect permitting the displacement of the abdominal organs into the thorax. But even among the acquired cases it should be considered that the weakness in the structure of the muscle or the patency about a normal hiatus may be congenital in origin and predisposes to the occurrence of hernia at some later period of infancy or childhood.

Anatomically diaphragmatic hernia is diagnosed as true or false; the condition is spoken of as true hernia when a sac is present and false when absent. In the false hernia the sac is absent because of a defect in the formation of the pleuroperitoneal membrane. In true hernia the pleuroperitoneal membrane envelopes the prolapsed abdominal organs. The occurrence of false hernia is much more frequent than that of the true variety. According to Eppinger's statistics the "false" type of diaphragmatic hernia is eight times as frequent as the true. False herniae occur more frequently on the left side, while true herniae are relatively more frequent on the right side. In false herniae the defect in the diaphragm varies from a small

content of the organs contained in the thorax. It is always possible that strangulation or volvulus of intestinal contents may occur. Gastric ulcer with resultant hemorrhage has already been mentioned. Symptoms indicating a chronic ileus may be present. The physical signs are of importance; in older children the simultaneous symptoms on the part of the respiratory and digestive organs should arouse suspicion. Most important of all is the x-ray and fluoroscopical examination.

Reference has already been made to the differentiation of hernia from relaxation of the diaphragm. This is in some cases difficult and at times impossible.

Prognosis.—Many of the newborn infants suffering from congenital diaphragmatic hernia die during the first days of life. In other instances patients may continue to be in comparative comfort to the tenth or twentieth year or even well into adult life. The most frequent cause of death is strangulation of the prolapsed intestine.

Treatment of Diaphragmatic Hernia.—The treatment of the symptoms of diaphragmatic hernia which are observed shortly after birth, especially symptoms as dyspnea and vomiting, may be attempted by placing the body in a semi-inverted position, passing a stomach tube to remove the gastric contents.

Radical surgical methods should give place to conservative treatment during early infancy. Later in life radical surgical treatment may be tried. I shall not go into the surgical details. In some, laparotomy is performed; in others, thoracotomy, though Hedblom reports that thoracotomy has yielded a somewhat lower mortality than laparotomy. A combined thoracolaparotomy may be necessary to effect reduction and closure. But such a combined operation has considerably increased the operative hazard. Surgeons advise that, if possible, the hernia rings should be sutured. In a few cases of large or recurrent hernia, openings have been successfully closed by fascial transplants or muscle plastic. Following operation fluid tends to accumulate and pneumonia may develop. Operation is absolutely indicated when strangulation of the dislocated bowel occurs. While a number of successful operative cases are re-

shoe kidneys and undescended testes are frequently associated with congenital diaphragmatic herniae. Lauenstein records that in one of his cases, which was operated upon and died shortly thereafter, numerous malformations were discovered, among which may be mentioned stricture of the left ureter, a retained testis and malformation of the mesentery. In another case he records in association with diaphragmatic hernia a microcephalus with a funnel thorax.

Symptomatology.—In the newborn, symptoms shortly after birth may be severe and acute. Cyanosis and dyspnea are usually the most marked symptoms. The infants are very restless and frequently die during the first days of life. In the left-sided herniae dextrocardia is nearly always present. It has already been pointed out that dextrocardia occurs in eventration as well as in hernia. Children with diaphragmatic hernia show their distress by an anxious moaning and crying, though this may be absent. While the respiratory and circulatory symptoms may be directly proportionate to the extensiveness of the defect in the diaphragm, nevertheless there are undoubtedly numerous instances where infants were born with congenital diaphragmatic hernia and reached adult life. In older individuals the symptoms, if any are present, may be referred to the cardiac and respiratory organs, though later on symptoms may be referred to the gastro-intestinal tract. Constipation, dyspeptic symptoms and stationary weight are frequently observed in childhood. Hematemesis as the result of gastric ulcer is not frequent in infancy, though it is not uncommon in adults, probably due to a circulatory impairment. Retraction of the abdomen and difficulty in swallowing, due to pressure on the esophagus or malposition of the stomach, may be present.

Diagnosis.—The results of physical examination vary and depend on the abnormal position of the dislocated viscera; also upon the degree of displacement of the lungs as well as upon the fluid contents and changes in the displaced hollow organs. Displacement of the heart to the right is mentioned again; on auscultation breath sounds are diminished or absent and the percussion note may be tympanitic or dull, depending upon the fluid

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ported in the literature among young children, nevertheless the operative mortality is high. Detailed surgical descriptions and operative methods are fully described in surgical manuals.

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quickly learned that "we were confronted by a new disease," of which the history of medicine had taught us nothing.

Each of these two great epidemics was followed by a disposition to regard prevalent infections of nonspecific type, especially when involving the upper respiratory tract, as influenzal. For a generation after the epidemic of 1889-1892 the term "la grippe" was applied to almost every type of upper respiratory infection from the common coryza to acute bronchitis. Occasionally epidemics of such infections were followed by numerous cases of pneumonia. Since the epidemic which occurred during the Great War and immediately thereafter, influenza or the colloquial "flu" has been used as a satisfactory diagnosis for many forms of infection involving the upper respiratory tract. The term has been used carelessly and has been extended to cover some conditions unrelated to influenza, for instance, the diagnosis "intestinal flu" hardly attains the dignity of a working hypothesis. It is more likely to be a cover for ignorance or indolence. In the course of epidemics cases may occur with predominant gastro-intestinal symptoms, though these are not frequent. Gastro-intestinal symptoms when due to influenza are commonly associated with the usual symptoms of the latter.

There have occurred in the past decade isolated outbreaks in epidemic form of a disease resembling influenza as it was manifest in the pandemic of 1918-1920. No epidemic of so-called "influenza" in this period has exhibited the same virulence or the widespread dissemination of the great epidemic. Bacteriological and serological proof for the diagnosis of influenza is not available. Even clinical features of diagnostic import are not pathognomonic, yet we do see from time to time isolated cases or groups of cases and epidemics of some extent so reminiscent of the typical disease as to justify the diagnosis of influenza.

This diagnosis is usually made when cases characterized by coryza, a troublesome dry cough, a feeling of tightness or pain in the upper substernal region, severe headache, marked depression, physical and mental, an abrupt rise of temperature,

CLINIC OF DR. JAMES G. CARR

EVANSTON HOSPITAL

INFLUENZA

THE great pandemic of 1918-1919 left a vivid impression of characteristic clinical manifestations. A recrudescence of the disease occurred in the winter of 1919-1920, less severe in type, less widespread, but easily identified with the disease which had so recently prevailed in epidemic form. Descriptions of the extensive epidemic which prevailed throughout the world from 1889 to 1892 do not include some of the most striking features of the disease seen in 1918-1920. The former epidemic was milder, attacked by preference a different age group, did not show the hemorrhagic bronchopneumonia, the high incidence of empyema, the terrible mortality from pneumonia among young adults. The mortality was said to be highest among the aged, the infirm and children.

The statement of Leichtenstern regarding the physicians of his own day that "the medical profession of our day found itself confronted by a new disease which up to that time had been known to them only in the history of medicine," is essentially true of the profession as it faced the problems of influenza in 1918, but one important difference may be noted. It was true that physicians of the late eighties were almost devoid of personal experience with influenza as an epidemic of world-wide character. No such epidemic had been known since 1847-1848. However, the outbreak of 1889 was not unique in its manifestations. It presented standard clinical findings recorded more than a generation before. The terrible visitation which raged at the end of the war presented features not hitherto described, characteristic clinical and pathologic results of the virus of influenza. While we fancied we knew influenza we

These 3 cases illustrate the clinical course of a mild influenza. Cases I and II ran courses of three or four days with fever, headache, cough, and generalized aching. The third patient had a more severe attack, with higher temperature and more prostration. After forty-eight hours of illness the temperature fell to normal for some six hours, then showed a moderate rise. Profuse sweating also occurred. The leukocyte count was normal in all three. The third case presents a familiar phenomenon in the course of the disease, the recrudescence of fever and symptoms after an initial fall. Often this second rise marks the beginning of pulmonary involvement, but this is not invariably the case. It may occur in the course of uncomplicated influenza.

Case IV.—A nurse, aged twenty-one, was admitted to the hospital on December 20th. Three days prior to entrance she began to have headache and

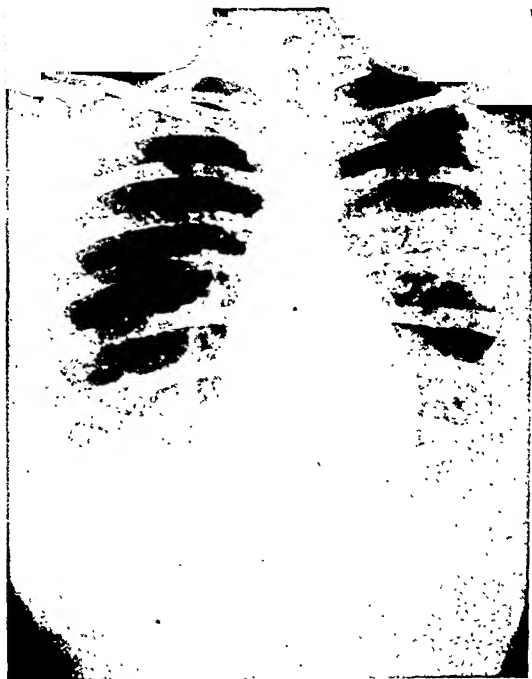


Fig. 79.—Showing pneumonic process on left side.

dizziness. On the following day she felt feverish. The headache persisted. There was no cough. Upon admission the temperature was 102 F., pulse 100,

101 to 103 F., without a rise in the leukocyte count, appear in numbers within a short time. If an outbreak of such character is followed by the development, in many such cases, of pneumonia in which the striking characteristics of lobar pneumonia are lacking, the view that the epidemic is influenzal is likely to be accepted.

Since about the middle of November a mild epidemic of this sort has prevailed in our community. Many such cases have been treated at this hospital. Most of the patients have presented only the clinical course of influenza without the development of pneumonia. The incidence of the influenzal infection among the nurses has been considerable. Examples of various degrees of infection as far as respiratory disease is concerned, including various types of pulmonary involvement, have been chosen for presentation. The case histories of these patients will be read in abstract and discussed.

Case I.—A young woman, aged twenty-five, was admitted to the hospital on January 2, 1933. Three days prior to admission she noticed fever and headache and began to cough. The cough was nonproductive. On admission temperature was 100.6 F., pulse 96, respirations 26. On the following day the temperature was 99.4 F., and after the third day in the hospital there was no fever. Leukocyte count was 4150. There was no evidence of pulmonary disease. The patient was discharged on the fourth day of normal temperature.

Case II.—A nurse, aged twenty, entered the hospital within a few hours of the onset of her illness. She had quite suddenly developed headache, cough, and generalized muscular aching. The temperature was 100 F., pulse 100, respirations 22. The white count was 6150. The lungs were clear. On the following day temperature was 101 F. Two days later this was normal. On the fourth day of normal temperature she was discharged.

Case III.—A woman, aged twenty-five, was admitted to the hospital on the second day of an illness which began with a slight head cold, cough and chilly sensations. On the day before admission the headache was severe. She also had backache. The temperature was 103 F. On the morning of admission temperature was 104 F. Upon admission, later this same day, temperature had fallen to 100 F., pulse was 88, respirations 20. Leukocyte count was 8150. Except for a few coarse bronchial râles the lungs were negative. On the day after admission the temperature was twice found below normal, rose to 99.2 F. at 8 P. M. and to 100 F. on the following morning. Following this rise of temperature she perspired profusely. Thereafter the symptoms subsided promptly and on the fourth day of normal temperature she was discharged.

admission. For four days the temperature continued at a level of 101 to 103 F. During the next week the symptoms and fever slowly abated. On the twelfth day in the hospital the temperature was normal. On the fifteenth day the temperature began to rise. Evidence was found of fluid at the left base. The temperature remained about 100 F. Two days after the onset of the remission 400 cc. of clear fluid were withdrawn. Four days later the temperature was normal and this was followed by satisfactory convalescence.

Case VII.—A young woman, aged twenty, was admitted to the hospital on the second day of an illness characterized by fever, generalized aching, cough

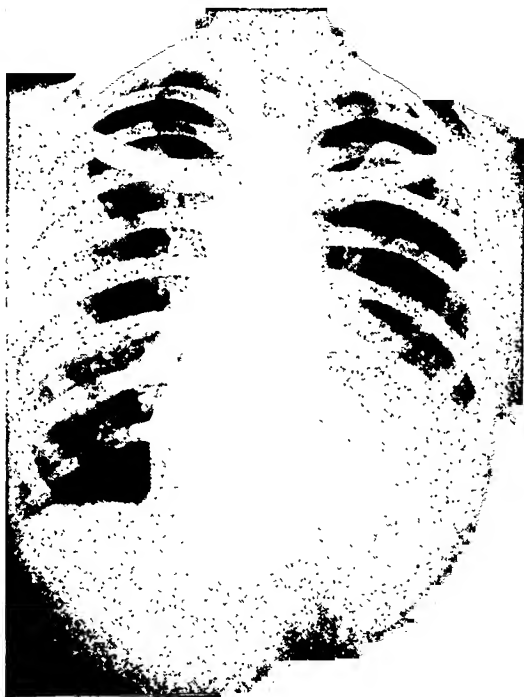


Fig. 80.—Pneumonic process at left base.

and malaise. Temperature was 101.5 F., pulse 132, respirations 20. Leukocyte count was 18,000. There were no physical signs of pneumonia. On the next day the temperature was 102 F., pulse 130, respirations 30. In the afternoon it was noted that "examination reveals an impairment of resonance at the left base posteriorly and in the axilla, but no conclusive signs of consolidation"; at 9 o'clock on the evening of the same day "a definite patch of consolidation and bronchophony, and bronchial breathing was found over the left side a little below the lower angle of the scapula." The patient was quite sick, restless and anxious about herself. She was placed in the oxygen tent. The roentgenological

respirations 20. Physical examination revealed no evidence of pulmonary disease. On the next day, the fourth of her illness, the temperature was 100.6 F., pulse 86 and the leukocyte count was 6850. The urine was normal. There were still no physical signs of pulmonary disease. At this time she had a slight cough. On the fifth day the highest temperature was 101 F. Physical examination was still negative but an x-ray plate (Fig. 79) was reported as showing "a patch in the left chest, in the third, fourth and fifth interspaces which looks like the terminal stage of a resolving patch of pneumonia or the beginning of a pneumonia." Upon the following morning a clinical note records "a patch of fine râles at the end of inspiration in the left axilla below the fifth rib." Thereafter the maximum daily temperature for four days was 101 F. (once 101.6 F.) and the minimum was normal at least once daily. Two leukocyte counts made at the height of the disease showed less than 7000 at each count. On the eighth day of hospitalization the maximum temperature was 99.8 F. On the ninth day, temperature was normal all day. Except for elevations to 99.4 F. on two different occasions no further fever was observed. The patient made an uneventful convalescence.

Case V.—A nurse, aged twenty-two, was admitted as a patient January 21, 1933. For a week she had noticed a slight cold. Three days before admission she became hoarse, began to cough, felt feverish and noticed a heaviness in her chest. Upon admission her temperature was 101.2 F., pulse 112, respirations 28, blood pressure was 115/72. She did not appear acutely ill. There was a frequent hacking nonproductive cough, but physical signs of pulmonary disease were not discovered. On the afternoon of the 23rd suppression of the breath sounds was noted at the left base posteriorly. On the following morning it was noted that "fine, moist râles, fairly numerous, are heard about the lower angle of the left scapula. The findings are strongly suggestive of bronchopneumonia." Later on the same day a roentgenological diagnosis of influenzal pneumonia on the left side was made. The cough persisted and was very troublesome. The temperature fell slowly, reaching normal on the seventh day after admission to the hospital.

Case VI.—A married woman, aged forty-two, was admitted to the hospital on January 5, 1933. She had developed a cold shortly after Christmas. On January 2nd she felt badly. A temperature of 101 F. was discovered. She was coughing and her chest was quite sore. On the following day the temperature subsided, almost reaching normal. Improvement was of short duration. Within twenty-four hours a sharp pain was felt in the left side. The cough increased and during the evening she expectorated a rusty sputum. Upon admission the temperature was 101.4 F., pulse 120, respirations 30, blood pressure 110/72. Her appearance was that of a person acutely ill. Respiration was accompanied by slight respiratory grunt. The lips and nails were cyanotic. Dulness was determined over the left lower lobe. This was accompanied by fine râles, bronchial breathing, bronchophony, increased tactile fremitus. The leukocyte count was 27,850. The blood culture was positive for *Streptococcus viridans*, which had previously been found in the sputum. The clinical course was that of a patient who was seriously ill. She was put in the oxygen tent shortly after

of influenza and the noninfluenzal lobar and lobular pneumonias which occur in the epidemics." He refers to Leichtenstern, who differentiated between early and late pneumonias, whereby the first was regarded as the pneumonic form of influenza, while the latter appeared as a complication of milder catarrhal disease. Gsell believes that the late pneumonias which supervene upon a previous febrile influenza are usually recognizable as the result of secondary influenza and states that "influenza prepares the ground by means of toxic effects on tissues and vessels." He also quotes Massini thus, "grippe not only produces a general disposition to other diseases but also modifies the soil so that these diseases run a course different from what we have known."

The criteria laid down by Gsell for the diagnosis of influenzal pneumonia are these:

"1. The beginning of the disease is never abrupt as with croupous pneumonia. Particularly is the initial chill lacking.

"2. The temperature falls by lysis; above all it never shows the expected crisis.

"3. The course is often marked by especial severity of the toxic phenomena.

"4. Friedmann could demonstrate in influenzal croupous pneumonia other bacteria than the type found in genuine lobar pneumonia. . . .

"5. Influenzal pneumonia shows an anatomic picture with distinct peculiarities. . . ."

If we review Cases VI, VII and VIII in which the etiologic diagnosis is most difficult to determine, it may be pointed out that Case VI presented the four clinical criteria. Case VII presented three of the clinical criteria, and Case VIII only the first, third and fourth of the criteria mentioned. In this case the conditions of the fourth criterion were not adequately met.

The leukocyte count is of less importance than the criteria mentioned. The initial influenza usually presents a count well under 10,000. With the onset of the pneumonia the count usually rises. Where suppuration ensues as in an empyema or a purulent bronchial pneumonia with multiple abscesses, the

plate made the next morning is shown in Fig. 80. Through forty-eight hours the temperature remained about 100.5 F., the pulse rate slowly fell from 130 to 100. During the next two days both temperature and pulse rate were declining and the respirations fell to 24. On the sixth day after entering the hospital the temperature and pulse rate were normal. A leukocyte count of about 15,000 persisted for several days, but at the time of discharge, fifteen days after admission, the white count was 8600. Examination of the sputum shortly after admission had shown the pneumococcus type III.

Case VIII.—A woman, aged thirty-four, unmarried, was admitted to the hospital after four days' illness. During the past three weeks she had been known to have a slight daily rise of temperature and she had been under investigation for a possible tuberculosis. Four days before admission she began to cough, felt ill and took to her bed. The symptoms did not abate. She grew worse and had some nausea and vomiting and on the day before admission severe pain in the right side, with simultaneous expectoration of blood-streaked sputum. Her temperature rose to 103 F. On the day after admission signs of pneumonia, typical consolidation of the right upper lobe, were clear. The leukocyte count was 4200. Two other counts were respectively 9500 and 6200. Throughout the course of the disease the patient presented a notably low blood pressure, as low as 70 systolic. This feature along with the history led us to think of a possible Addison's disease as responsible for the clinical picture prior to the acute illness, but no confirmatory signs were present. Bacteriological study of the sputum was fruitless. Gram-positive cocci in pairs and chains were found in the sputum, but the type could not be determined. Death occurred on the third day in the hospital.

The etiologic diagnosis of the last 3 cases presents difficulties. In each, certain features point to the presence of a lobar pneumonia of the usual type. The onset following upon an upper respiratory infection and the development of consolidation without the characteristic chill and abrupt onset of lobar pneumonia, which the cases present in common, are the features which favor a diagnosis of an influenza-pneumonia. The onset of pneumonia without chill but with pain suggestive of pleurisy was common in 1918-1920. Furthermore, these cases occurred in the presence of an epidemic of a disease regarded as influenza. The etiology of the complicating pneumonias and the relationship of the secondary pneumonia to the primary disease have been the subject of almost endless discussion. We quote from a recent monograph by Gsell of Zurich, "The difficulty is not in the determination of the pulmonary disease but in the distinction between the pneumonia

to suspect the presence of scattered pneumonic areas but no physical evidence of such could be elicited. Neither dulness nor bronchial breathing could be discovered. Temperature fell by lysis on the sixth day. Throughout the course the patient complained of extreme headache with insomnia and much pain in the muscles of the back and legs. Finally, a maid in the family developed an upper respiratory infection, fever, cough, headache and general muscular pain.

On December 10th, a boy of sixteen was seen with Dr. G. F. Weinfeld. The patient had noticed a slight cough on the morning of December 8th, notwithstanding which he had participated in a strenuous workout with the high school swimming team. On December 9th when examined he had a slight cough, a mild rhinitis, and a temperature of 101 F. He was not regarded as seriously ill. On the morning of the 10th the clinical picture was that of a serious illness. The boy was toxic, listless and bringing up a considerable quantity of hemorrhagic sputum. Temperature was 102 F., pulse 120, leukocytes were 32,000, with 90 per cent of polymorphonuclears. Over the right base the breath sounds were suppressed and the resonance was definitely impaired. Type I pneumococci predominated in the sputum. The urine showed albumin and was strongly positive for acetone. The patient was placed in the oxygen tent. On the following morning the temperature was normal but before noon he had a severe chill followed by a rise in temperature to 103 F. The pulse was about 110 to 120. Findings over the chest were unchanged. During the night he had a profuse perspiration. During most of the next day the temperature was normal, the pulse about 90 and respirations 22. Late in the afternoon he had another chill followed by a rise of temperature to 103 F. He also had sharp pain in the right side. When examined on the 13th there was dulness over the right side with distant tubular breathing. Pneumonia, probably accompanied by pleural effusion, was diagnosed. Following this examination he improved steadily, though bloody expectoration persisted for three days. Convalescence was complicated by an acute frontal sinusitis of the left side.

counts are likely to be quite high. A count so low as was found through the course of the illness in Case VIII is typical of neither type of pneumonia, influenzal or pneumonic. It may plausibly be explained as one evidence of poor defensive mechanism.

One important feature which must be considered in the differential diagnosis of influenzal bronchopneumonia is left for discussion. The pneumonias under consideration occurred during the course of an epidemic of upper respiratory infection which simulated influenza. This may be regarded as probable evidence of the influenzal nature of complicating pneumonias. The appearance of an epidemic of influenza followed shortly by an outbreak of cases of atypical pneumonia is significant. It is interesting to note that since the epidemic of upper respiratory infection has subsided, the incidence of pneumonia has decreased. We have seen few primary pneumonias this winter.

While the epidemic was at its height we had an interesting experience in a family treated by Dr. Garner. A boy of fourteen was seen by Dr. Garner on December 1st, at which time the patient complained of headache and backache and had a temperature of 101 F. The symptoms were unchanged until December 4th, upon which date a chill occurred followed by a rise in temperature to 103.4 F. The leukocyte count was 7000. About the lower angle of the left scapula the resonance was impaired and a few fine crackling râles were heard. The temperature continued moderately high, 101 to 103 F., and the cough, nonproductive, persisted. On the eighth day large moist râles rather suddenly developed over the entire left lung anteriorly and posteriorly. The temperature on this day varied from 99 to 102 F. After the tenth day the temperature was normal. About this time the father of the family had a mild attack of upper respiratory infection. A few days later the mother had a chill while away from home. Upon arriving at home her temperature was 102 F. Over the right upper lobe anteriorly fine dry râles and some moist râles could be heard. Later these were scattered over both lungs. The fine dry râles, characteristic of terminal bronchial obstruction, prevailed. The temperature range was from 101 to 104 F., which led us

is reasonable in so far as the clinical picture of the case as diagnosed is clearly similar to that of the epidemic type of influenza. If the clinical manifestations of a particular local epidemic are mainly such as are characteristic of influenza as encountered during an extensive pandemic and are usually similar to each other in the course of the local epidemic it would appear justifiable in the present state of our knowledge to assume to accept such an epidemic as one of influenza. Such a conclusion must base its support upon the clinical likeness of the epidemic under consideration, to the course of the disease in the great outbreaks. An explosive onset of a particular epidemic adds to the probability of influenza.

The abrupt onset with headache, fever, backache and dry cough, the rather abrupt fall of the fever about the third or fourth day, the usual absence of a rise in the leukocyte count, the tendency to a short exacerbation of the symptoms after the first fall of the temperature and the frequent occurrence of pneumonia of insidious onset, often with poorly defined physical findings, running an atypical course without the presence of typical pneumococci in the sputum, are the features of the disease upon which the diagnosis is based.

The prognosis in the group of cases described was almost uniformly good. Between 30 and 40 patients were in the hospital within six weeks, of whom 10 or 12 had pneumonia, only one death occurred. At the same time the disease was widely prevalent throughout the city with a notably low mortality. An occasional case revealed a virulence like that of the typical influenza bronchopneumonia. One patient seen at another hospital had suffered from a "cold" for several days. On Saturday he abruptly worse after-aminat. til the e bacillus w.

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It may seem presumptuous to present as a case of influenzal pneumonia one in which the type I pneumococcus predominated and the leukocytosis was very high. The profuse bloody expectoration ensuing upon a single day's illness which started as a coryza, followed by symptoms of toxemia and early signs of consolidation without chill, the abrupt fall of the temperature to normal, with simultaneous fall of the cardiac and respiratory rates followed by the recrudescence of symptoms twice, after such a drop in temperature, associated with severe chill and sharp rise of fever, the failure to discover the characteristic signs of lobar pneumonia and the eventual occurrence of a frontal sinus infection during convalescence indicate that this illness was not due to a pneumococcic infection.

A number of cases have been presented which occurred during an epidemic. Various types of the epidemic disease have been presented, including simple influenza and different manifestations of pulmonary involvement, bronchitis, bronchopneumonia, pleural effusion and pneumonia with signs of the lobar type of irregular course.

In 2 cases convalescence was prolonged because of a persistent tachycardia associated in both cases with minor electrocardiographic changes, and in one case with persistent fever. Both recovered clinically, although one patient had an abnormal electrocardiogram when she left the hospital. Myocardial weakness as a result of influenza has been noted clinically many times. In recent years this condition has often been demonstrated in the electrocardiogram. The tendency to myocardial involvement in the course of influenza should not be forgotten. Often the sole symptom is the general weakness associated with a marked disinclination to physical exertion. Prolonged rest with careful oversight of the patient is the treatment.

Doubtless it will be noted that practically no complications are referred to except those involving the respiratory tract. This indeed is the rule in the milder epidemics of influenza. It is true that a great variety of complications were seen at the height of the epidemic in 1918-1920. Hardly an organ in the body escaped involvement at one time or another. Since the

upon clinical findings is reasonable in so far as the clinical picture of the cases so diagnosed is clearly similar to that of the epidemic types of influenza. If the clinical manifestations of a prevalent local epidemic are mainly such as are characteristic of milder cases encountered during an extensive pandemic and are notably similar to each other in the course of the local epidemic, it would appear justifiable in the present state of our knowledge or ignorance to accept such an epidemic as one of influenza. Such a conclusion must base its support upon the clinical likeness of the epidemic under consideration, to the course of the disease in the great outbreaks. An explosive onset of a particular epidemic adds to the probability of influenza.

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Particular interest attaches to these occasional virulent cases

to accept this view of the etiology of influenza, but their position is now stoutly opposed. In 1921 Malloch in a discussion of this subject used these words, "How are we to discuss these scattered cases? In the light of our present knowledge it is impossible to do this, as we do not know the cause of the disease and, as various investigators have shown, small or even large epidemics simulating influenza in the closest way may be caused by the pneumococcus, streptococcus, micrococcus catarrhalis and other organisms."

Massini in a monograph on influenza makes the statement, "that we can indeed accept with some probability that the virus of grippe has not been discovered, that it is a filtrable virus," and Gsell states, "after the discovery of Pfeiffer's bacillus it was believed that bacteriologically it would be possible to differentiate the pneumonic cases of grippe, but the skepticism regarding the etiological significance of this bacillus in the last decade and the frequent failure to demonstrate the same and the occurrence of mixed infections in fatal cases now allows no decisive significance to the bacteriological diagnosis." In a recent review MacDermott vigorously questions the relationship of Pfeiffer's bacillus to influenza and includes a quotation from the literature reading thus: "Whatever is the cause of influenza it is certainly not Pfeiffer's bacillus. If the infection is due to a common virus Pfeiffer's bacillus is not even a common secondary invader."

If we are to use the diagnosis of influenza in a strict sense to include only such manifestations of disease as appeared in the typical cases during an epidemic of frank influenza, we may be questioned when we speak of the cases here described as cases of influenza. The marked prostration, the abrupt rise of temperature to 103 or 105 F., the bradycardia, the frequent enlargement of the spleen, the hemorrhagic tendency with epistaxis and bloody sputum, the early development of ominous pulmonary symptoms and massive pleural effusions are rarely met with in the minor epidemics.

Are we justified in the diagnosis of influenza in these minor cases? We may reply that the diagnosis of influenza based

since they are regarded by some authorities as putting the stamp of influenza on an epidemic. Typical instances of influenza are most likely to prevail at the onset or the height of an epidemic. Their appearance in isolated instances is fairly good presumptive evidence that the true virus of influenza is prevalent and is causing any epidemic which may be active at the time.

In the treatment the prevention of the spread of the disease is the first consideration. Isolation of the patient, disinfection of the sputum, masking of attendants are of fundamental importance. It is true that the usual mode of onset of influenza is characterized by the sudden appearance of cases scattered throughout a community. This initial diffusion of the disease defeats the purpose of many of our prophylactic procedures, yet these should be carried out strictly. Undoubtedly they help to lessen the incidence of contact infection. Further treatment is confined to symptomatic remedies, particularly to relieve the headache, the backache, cough and insomnia. Sufficient fluid, an adequate and easily digestible diet, and rest in bed through at least three days of normal temperature are fundamental features of therapy. Return to work should be determined by the patient's condition, the nature of the work performed, the state of the weather. Early exposure or undue fatigue may be followed by a relapse and pneumonia. Such events are often extremely serious. Influenza apparently creates no immunity, rather, as has already been suggested, it deprives the body of normal protective powers. It is not intended here to discuss the treatment of pneumonia. I have indicated the prophylactic measures that should be employed in order to avoid the onset of pneumonia. While I am not now undertaking so large a task as the discussion of the treatment of pneumonia in general, I may be pardoned in pointing out that we have referred in several cases to the use of the oxygen tent. It is our opinion that modern methods of administering oxygen have been of great service in the treatment of pneumonia, have eased the patient during the course of his disease and lowered the mortality, and we feel that this remedy should be employed to a much greater extent than it now is.

pital. There were ten such syncopal attacks during the last five weeks. Vomiting occurred for the first time five weeks ago and is usually before meals. There is usually a great deal of retching. This apparently also had no relation to food or time. There was no gross blood noted in the vomitus. Her appetite has been poor; she has been somewhat constipated and has lost some weight but does not know how much, all in the last five weeks. At the outset there was a tarry stool. There has been a slight cough of late, productive of a sero-mucoid expectoration but no evidence of blood. She has had a slight dyspnea and there have been occasional chilly sensations during the last few weeks. There has been no edema of the feet and no other noteworthy cardiac findings. She has urinated twice each night for the last five weeks, but other than that her genito-urinary system was essentially negative. The manifestations of her nervous system other than noted are of no clinical importance.

Her medical and surgical history are negative. She has been separated from her husband for the last six months. Her mother died of heart disease, her father of diphtheria. Two sisters and one brother are living and well. Five children are living and well; no miscarriages.

Her menstrual history was regular until five weeks ago and she has menstruated twice during this last month. There is no history of venereal disease and her habits are normal.

Physical examination at that time revealed an anemic, white female, about forty-seven years old, with a lemon-yellow tint to her skin but not appearing acutely ill. Her temperature, pulse and respiration were normal. There was a generalized anemia of the body manifested by marked paleness of the conjunctivae and mucous membranes. The eyes reacted to light and accommodation. The thyroid was not enlarged. The lungs were essentially negative, as was the heart except for a slight hemic murmur.

There was tenderness in the epigastrium but no corresponding palpable mass. The abdomen was scaphoid, the liver was not enlarged, the spleen not palpable, and the rest of the findings in the abdomen were of no clinical importance.

There was no edema of the extremities; the reflexes and other neurological findings were all within limits of normal. There were no petechial hemorrhages to be found anywhere on the body.

Her blood count was hemoglobin 32, red blood cells 2,490,000, white blood cells 5400, with a differential count of 77 per cent polymorphonuclears, 2 per cent eosinophils, 23 per cent lymphocytes, 3 per cent monocytes. There is an anisocytosis, poikilocytosis, macrocytosis, achromia, and polychromatophilia.

The stools showed a trace of occult blood. The urine was essentially negative. The blood Kahn was negative. The blood chemistry showed no noteworthy findings. The blood culture was negative after five days.

The patient ran a slight temperature, 99.5 F. at its height, the pulse was not rapid and the respirations were normal. The blood pressure measured 110 systolic and 70 diastolic.

In view of the clinical picture it was thought best to put the patient on ulcer management. During the course of this observation the occult blood disappeared from the stool and subsequent blood examination showed no improvement in the blood. Further investigation revealed that the bleeding time and

CLINIC OF DR. SIDNEY A. PORTIS

MICHAEL REESE AND COOK COUNTY HOSPITALS

ANEMIAS OF GASTRO-INTESTINAL ORIGIN

THIS morning I would like to present to you 4 cases which are of profound interest to the gastro-enterologist. Each of them typifies a certain group of cases and their early recognition is of vital importance to the welfare of the patient. Anemias of gastro-intestinal origin have been known for a long time, but their clinical importance has not been sufficiently emphasized and many of these patients go unrecognized for a period of months or years until they produce profound exhaustion of the hemopoietic organs and frequently produce irreparable damage.

Case I.—The first patient I would like to present is a woman, R. K., aged forty-seven, who entered the hospital on November 5, 1932. Her examining room diagnosis was malignancy, and judging from her appearance it was a justifiable presumptive diagnosis. However, her main complaints were those of vomiting, vertigo, headaches, syncopal attacks, weakness and epigastric pain. She stated that she was perfectly well until five years ago when she experienced for the first time an epigastric distress manifested as a feeling of pressure, lasting from fifteen minutes to one hour, which radiated across the left costal margin and then between the scapulae. This symptom occurred on three occasions daily for the first three days; sometimes it would be more frequent, then she would be free from symptoms for about a week or ten days, followed by similar attacks. She had always been relieved by taking a small amount of sodium bicarbonate. These attacks apparently had no relation to food or time, and for the last five years they have recurred more or less intermittently with the same intensity as that at the onset. There was no nausea or vomiting, no blurring of vision. There was no precordial distress, no sensation of chest constriction or radiation of pain down the left arm.

About five weeks prior to entrance, while riding on a street car, she suddenly fainted and remained more or less in syncope for five to ten minutes. She then regained consciousness but was very dizzy, became weaker and weaker, remaining in bed for the past five weeks and was then advised to enter the hos-

accentuation of the second aortic, however with a blood pressure measuring 118 systolic and 78 diastolic. He was definitely tender over the gallbladder region. His liver was just slightly palpable and there was no other noteworthy tenderness nor tumefactions in the abdomen.

His laboratory and x-ray investigation revealed on Ewald and motor meal the absence of free hydrochloric acid, but a total acidity of 10. The usual test for pepsin revealed a normal peptic activity. Subsequent observation with a Rehfuess fractional method, alcohol test meal, neutral red and histamine injection revealed a complete absence of free hydrochloric acid.

His cholecystogram revealed evidences of a pathologic gallbladder with several calculi. His urine was essentially negative. The stool was negative for occult blood on a meat-free diet. The Wassermann test was negative. His basal metabolic rate was within limits of normal. His fluoroscopy of the chest other than a slight enlargement of the heart was within limits of normal. His stomach, duodenum, small and large bowel showed no noteworthy pathology to explain his present symptom complex. His hemoglobin was 60, his red count 3,436,000. The white count was 6800. His differential was 36 per cent mononuclears, 1 per cent large mononuclears, 57 per cent polymorphonuclears, 1 per cent eosinophils. There was some poikilocytosis and anisocytosis. His blood findings other than that were of no noteworthy significance.

The important consideration in this particular individual's case is an association of an achlorhydria, a pathologic gallbladder and a secondary anemia. It has been known clinically for some time that this is not an uncommon clinical picture. It is also known that these patients do not respond well to ordinary procedures of medical management and they very frequently develop a true primary anemia. Clinical experience has taught us that surgery in these cases is definitely indicated and cholecystectomy seems to bring about a cessation of the onward course of the disease and prevents in most of these cases the development of a true primary anemia. Other clinical investigators have watched these patients without operative interference and have seen the development of a so-called "pernicious" type of anemia where no extirpation of the gallbladder has been made. The clinical significance of this group of cases has been very little understood and most of us who have seen this type of case have become convinced that something radical should be done to prevent the development of a true type of anemia. In this particular case cholecystectomy was done. The patient has now gone some five years after operation with a

coagulation time were within normal limits. The platelets were normally present and the fragility test showed no marked deviation from normal.

After a period of ten days, the stool being free from occult blood during this time, it was thought advisable to fluoroscope the patient. Gastro-intestinal x-ray revealed a negative stomach, a definitely and persistently deformed duodenal bulb, normal findings of the colon, and the cholecystogram was normal. Then an Ewald test meal revealed 43 free and 55 total acidity. The stomach had a normal emptying time.

What was the cause of this woman's severe anemia? The usual causes for anemia were eliminated and, therefore, we must confine ourselves to the view that this patient has had for a long period of time an oozing duodenal ulcer. She produced more or less exhaustion of her hemopoietic system and finally she was seized with an attack with a large hemorrhage and was then brought into the hospital for observation. Her clinical course has improved, following the giving of a blood transfusion and daily injections of 20 cc. of Wassermann-free whole blood given into the gluteal regions. She is now able to assimilate a full ulcer diet. Her general picture has markedly improved and now, five weeks after entrance, her hemoglobin is 59 per cent, red blood cells 3,930,000 and white blood cells 5800. She has been given liver extract and is now able to leave the hospital, apparently in a very much improved state.

Case II.—The next patient I would like to present is a male, aged fifty-nine, whose complaint is epigastric distress, headaches, tinnitus and vertigo. The last three or four weeks the patient has had epigastric distress manifested as a feeling of fulness coming on one-half hour after eating, lasting two to three hours, pressing upward, and causing some palpitation but no dyspnea. Belching relieves the distress. He has noticed also a very definite intolerance for fatty and greasy foods. He is not awakened at night. He has had some frontal headaches, associated with vertigo and tinnitus. He has felt a slight weakness. There has been no nausea or vomiting. There has been slight loss of weight. Inventory of his cardiorespiratory system other than noted is essentially negative. Genito-urinary system was essentially negative. His bowels move sluggishly and his appetite is fair. His wife died of an organic heart disease at forty-six. He has four children living and well. There was one therapeutic interrupted pregnancy for a mild tuberculosis. He denied a venereal history. He had measles but no other diseases of importance. He has had no surgery at any time.

He is active, sleeps well, drinks moderately of coffee and tea and does not use alcohol or tobacco.

Physical examination was essentially negative throughout except for slight

a carcinoma of the stomach. And such were the findings at operation. A resection was possible but, of course, the prognosis is always guarded. I would like to impress upon you this morning that the presence of an achylia or achlorhydria in carcinoma of the stomach is more or less of necropsy importance to me. Our diagnosis of carcinoma of the stomach must be made much earlier, before these so-called "late manifestations" which textbooks are so prone to point out for a conclusive diagnosis of malignancy, if we are to make any headway in the treatment of this almost fatal disease.

Case IV.—And finally I would like to present to you in this group of cases this morning a female patient, forty-four years of age, who one year ago began to have severe diarrhea, this associated with pain throughout the lower abdomen. She also noted that there was much blood and pus in the stools. This attack subsided, reappeared again six months later and then disappeared and recurred about a month ago. At this time the anemia was quite severe, and when seen in consultation she was ready to have a first stage operation for carcinoma of the colon.

There is nothing of noteworthy importance in this patient's past history. She has never had any acute diarrheas which might have precipitated a so-called "bacillary dysentery." There was no apparent evidence of an amebiasis, and fresh warm smears and subsequent cultures of the stool revealed no *Entameba histolytica*. The blood agglutination tests were negative for the various organisms of the bacillary dysentery group. This patient's blood count was 30 per cent hemoglobin, 2,500,000 red blood cells, 16,000 white blood cells with a definite polynucleosis, and it was because of her inability to get the barium down, given by mouth, beyond a certain portion of the colon and further inability to have the patient retain a barium enema that the diagnosis of carcinomatosis of the descending colon was made. However, a low proctoscopic examination and the roentgenological evidence certainly were suggestive of a diffuse ulcerative colitis. Subsequent proctoscopic, bacteriological and serological studies on the blood revealed that it was a typical case of so-called "non-specific ulcerative colitis." There was no evidence of stricture formation and it seemed to me at this time that the most urgent therapeutic procedure for this patient was a blood transfusion and not operative interference. This was done with an immediate response of the patient, and subsequent management with a high-vitamin, high-caloric, nonresidue diet associated with adequate amounts of bismuth, tincture of opium and atropine quieted down within a few days her marked diarrhea and within two weeks the patient was having only a few fairly well-formed stools a day and she was subsequently given the benefit of a vaccine treatment. This patient was told after she became clinically improved to have many of her diseased teeth removed, but like many of these patients who are improved she neglected herself and had a recurrence of her diarrhea. Then the teeth were removed, followed by another rigid course of

gradual improvement in his anemia, no evidence of return of free hydrochloric acid, and no tendency to develop a picture of true primary anemia.

Case III.—The next patient I would like to present is a man, fifty-three years of age, who has shown for the last ten months a gradual increasing weakness and some vague abdominal distress, not particularly modified by food intake or medication. This distress is more or less of a discomfort associated with no nausea, vomiting or belching. It is also noted during this time that there has been a gradual loss of weight. Inventory of his symptoms other than this was essentially negative. There is nothing of noteworthy importance in his family, venereal, medical or surgical histories. He had a slight hypertension of 170 systolic and 100 diastolic. He showed evidences of a generalized anemia. There was nothing of noteworthy importance on physical examination of the head, neck or chest. He was quite tender in the region of the epigastrium with a suggestion of a palpable mass. The liver and spleen were not notably enlarged. There was a slight loss of subcutaneous fat. There was no edema of the ankles at this time. The reflexes were normally intact.

His urine was essentially negative. His stool showed occult blood on a meat-free diet. His Ewald meal showed 15 free and 25 total, and his motor meal showed evidence of similar findings with no evidence of retention. His blood count showed a hemoglobin of 50 with a red count of 3,870,000 and 10,200 white cells with a normal differentiation. His coagulation and bleeding times were within normal limits. His Wassermann and Kahn were negative. The blood chemistry was essentially normal.

Fluoroscopy of the chest other than a slight enlargement of the heart showed no unusual findings. There was a persistent defect of the pars media and the greater curvature part of the stomach, showing posteriorly. It was nearer the antrum than the fundus. His stomach emptied within five hours. The rest of the gastro-intestinal tract was essentially negative, both fluoroscopically and roentgenologically. Cholecystography revealed no unusual findings.

So here we are presented with an individual in middle life who for some unknown reason gets a persistent upper abdominal distress associated with weakness and loss of weight, and the findings of a generalized anemia, associated with a positive and persistent occult blood in the stools, with still at this time no loss of free hydrochloric acid in the stomach, and roentgenologically demonstrated a definite filling defect in a more or less silent portion of the stomach. It is a typical type of a case that may be often presented to you and the first thing that comes to one's mind, even without evidence of an extensive laboratory and x-ray study is that the most likely clinical diagnosis would be

true of cirrhosis and hepatitis of other origins. We have shown a case this morning of secondary anemia with associated changes in cholecystitis. The exact rôle of any one of the manifestations in this last type of anemia is still debatable. And finally, we have anemias of gastro-intestinal origin which are associated with bacterial and parasitic infections. It has been thought by some that the anemia associated with the various tenia may not be considered truly a gastro-intestinal anemia but purely an incidental finding with the organisms in the gastro-intestinal tract. Blood destruction does not go on in the gastro-intestinal tract *per se*. There are many infections that have an anemia and an associated gastro-intestinal disturbance. These, however, are purely secondary and not primary manifestations.

Gastro-intestinal symptoms are very frequently associated with anemias. Some are primary, others secondary. Improvement in the anemia may be markedly delayed unless suitable diets are given—high-caloric, high-vitamin and well-balanced diet. The treatment of these anemias consists not purely of medication, but food plays an important factor in the restoration of a normal blood picture to that individual.

management and for the last five years this patient has been noticeably free of symptoms. The loss of weight, the severe anemia, the inability to get a proper roentgenological visualization of the colon led the attending physician to believe he was dealing with a carcinoma, but much more thorough clinical observation revealed the only possible diagnosis, that of so-called "nonspecific ulcerative colitis."

Many patients are operated for so-called "diffuse carcinomatosis" of the bowel who have nothing more than a long-standing chronic ulcerative colitis with thickening and stricture formation.

I have presented to you this morning four typical causes of anemias of gastro-intestinal origin, each more or less classical by itself, each calling forth a different therapeutic attack. There is no question in my mind, in the absence of obvious gastro-intestinal phenomenon, that many of our so-called "secondary anemias" may have a gastro-intestinal origin. The average clinical teaching is to recognize that the patient may have an anemia without any further search for the primary cause and frequently these patients are given hypodermic injections of one or more proprietary preparations and psychotherapeutically at least the patient is improved. I would like to outline to you in the few remaining minutes of this clinic some causes of anemia which might be considered as arising from the gastro-intestinal tract.

Their differential diagnosis is much too long to be taken up at this time.

The most common cause of anemia of gastro-intestinal origin is bleeding and this bleeding may occur anywhere from the mouth down to and including the anal region and particularly bleeding hemorrhoids. This bleeding may be associated with simple ulceration, carcinomata, telangiectasis, varices, or even the bleeding that occurs by diapedesis. Long-continued constipation or diarrhea may produce anemia. Changes in the stomach wall itself may produce an anemia with concomitant changes in the gastric secretion. Then, we have the anemias which may be called of gastro-intestinal origin because they are associated with liver disturbances. This is particularly

an epidemic and those which occur sporadically. In the former instance physicians are alert to the general signs and symptoms which may be common to that epidemic as characterizing the prodromal period of the disease, and spinal fluid examinations may be made upon suspicious cases, whereas in the latter the resemblance of the symptoms to other general infections may not arouse suspicion of poliomyelitis until evidence of paralysis occurs. On the other hand, as pointed out by Schwartz,⁷ a diagnosis of poliomyelitis is apt to be made without justification during an epidemic. The Harvard Infantile Paralysis Commission reported that of 187 calls received, only 123 proved to be poliomyelitis, the remaining 64 were infections—diarrhea, gastro-enteritis, influenza, vaccination, tuberculosis, epidemic meningitis, tuberculous meningitis, syphilitic meningitis and hysteria.

The signs and symptoms of the prodromal period do not differ greatly from those seen in any other general infection. The individual peculiarities of some of them and certain combinations of them may serve to call attention to the possibility of a poliomyelitis, and examination of the spinal fluid may assist in making a positive diagnosis.

According to the predominance of any one group of symptoms, meningeal, gastro-intestinal, respiratory, anginal, or merely febrile forms may appear.

Wickman called attention to the fact that in the Swedish epidemic of 1903, although the initial symptoms vary, they are similar in certain neighborhoods; that is, in one neighborhood meningitic signs predominate; in another, gastro-intestinal. The same observation was made in Germany in 1909, where in Hesse Nassau, Müller found severe intestinal symptoms in only a minority of his cases, whereas Krause reported about two thirds of the cases in Westphalia were affected with diarrhea, yet they were reporting different foci of the same epidemic. In some epidemics the respiratory tract is much more frequently involved than the alimentary tract, whereas in others vomiting, diarrhea and constipation occur.

As early as 1840 Heine⁸ described the symptoms of the

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THE DIAGNOSIS OF EARLY POLIOMYELITIS

POLIOMYELITIS is a systemic infectious disease, at times producing paralysis as a result of involvement of the nervous system.

In any particular epidemic the signs and symptoms occurring in the preparalytic stage of cases progressing to paralysis, and in the abortive cases, are in general quite similar. It is necessary to devise means of diagnosis before paralysis occurs to the end that adequate treatment may be instituted and preventive measures ensured.

The course of the disease may be divided into the incubation period, the period of systemic infection, variously called prodromal period (Römer¹) or stage of general invasion (Walshe²), and the stage of paralysis or invasion of the central nervous system. Draper³ has further divided the preparalytic period into a general systemic infection period, a latent period, and a "passage period." Walshe groups the two latter into a period of invasion of the subarachnoid space.

The duration of the incubation period is variously given, at times less than twenty-four hours (Leegard⁴), one to four days (Wickman⁵), one week (Müller⁶); Römer states it lasts at least five days; it is usually not more than ten days. Its average duration is about a week. According to Flexner the incubation period is subject to wide limits of fluctuation, in certain instances as short as two days, in others two weeks, possibly longer. The usual period does not exceed eight days.

The ease with which a diagnosis of poliomyelitis may be made before paralysis occurs differs in the cases seen during

"The most important prodromal symptoms are those connected with the nervous system. Without any definite psychological disturbance there is a certain degree of somnolence; rarely convulsions and tremors occur (they are noted more frequently by the older writers); of particular importance is a general tenderness of the whole person; this is characteristic and was observed by Heine, Duchenne and others. Even a light touch causes pain which is increased by passive movement, particularly if the spine be involved in the movement. Spontaneous pain occurs in the limbs and in the neck and back; the spine feels stiff. There may be tenderness to pressure of the nerve trunks."

Wickman says that as a rule the disease begins "quite suddenly with fever and malaise. Tenderness is a frequent and prominent feature. Pain, headache, stiffness of the neck and spontaneous pains in the limbs appear. In some cases vomiting and diarrhea are present, in others the disease commences with sore throat, coryza or bronchitis. These symptoms may constitute the whole picture. In others, after one or more days, paralysis appears."

Aycock and Luther⁹ describe the preparalytic stage as follows: "The patient is taken sick with fever, headache and a gastro-intestinal disturbance which usually consists of vomiting and constipation. Drowsiness and a desire to be let alone are also frequently observed. . . . On observation the child seems prostrated to a greater degree than the temperature, which is usually under 102 F., would indicate. The face is flushed, the expression is anxious and there is frequently pallor around the nose and mouth. The throat is mildly injected but not enough in itself to account for the child's condition. The pulse is usually rapid, out of proportion to the temperature." They then describe the additional signs, tremor, rigidity of the neck, stiffness of the spine with pain on anteflexion, hyperactive deep reflexes and *tache cérébrale*, which, combined, justify a probable diagnosis of anterior poliomyelitis.

To these general descriptions attention should be called to the course of the preparalytic or prodromal stage. Draper has

acute stage, including most of the signs and symptoms recorded to date. He said, "The disease attacks children who are healthy and well-developed at the age of from six to thirty-six months. Usually they have suffered from no illness previously, in some cases they have been somewhat unwell for a short time. The incidence is sudden, occurring with fever, congestion of the head, restlessness and, in short, symptoms of general irritation. . . . Sometimes the disease begins with vomiting, diarrhea or the appearances of acute rheumatism. Rarely one of the exanthemata seems to be at the root of the matter. Subsequently, there may be more or less severe convulsions, which may recur. . . . In other cases the paralysis appears after only slight general symptoms of fever which may be overlooked; the child goes to bed apparently healthy and is found paralyzed in the morning. . . . With the occurrence of paralysis the first stage of the disease is finished and it passes into its second stage."

It may be profitable to compare this general description to a few modern ones. Römer says, "The disease does occur suddenly without any prodromal symptoms (the paralysis of the morning) but this is exceedingly rare; usually there are symptoms for a variable length of time, one to seven days. The most common is fever of no great degree, which is sometimes remittent, sometimes continuous. The degree of fever and the severity of the prodromal symptoms generally have no relation to the amount of subsequent paralysis. The frequency of the pulse is increased, more than proportionately to the temperature. . . . Finally there is general malaise. Occasionally a rash is seen, very rarely herpes labialis (an important differential point with regard to cerebrospinal meningitis) and herpes zoster. . . . Quite frequently the respiratory tract is affected, the patient suffers from coryza with conjunctivitis; from bronchitis or even from bronchopneumonia. In some epidemics, *e. g.*, in our Hessian one, the respiratory tract was much more frequently involved than the alimentary tract which in other epidemics is a favorite seat of the initial symptoms; vomiting, diarrhea or constipation may occur.

order of appearance and combinations. Of these, fever is the most constant. Caverly¹² noted it in 221 cases of a total of 225; Armstrong¹³ in 100 of 100 cases; Wilson in 392 of 400; La Fétra and Schwarz¹⁴ in 684 of 745 cases. Most of the statistical reports are based upon the study of histories and, therefore, the facts are dependent upon the powers of observation and correctness of description of the examiners; such observations as are based upon obligatory records, as temperature, pulse, etc., often are accurate. At times one may interpret irritability as restlessness and vice versa. Caverly gives the frequency of one group of cases (69) as fever 69; pain 45; tenderness 42; vomiting 38; bladder disturbance 22; retention 17; incontinence 4, frequency 1; headache 19; chills 14; diarrhea 10.

Armstrong, from an analysis of 100 cases, notes fever 100; constipation 87; stiff neck 82; drowsiness 81; anorexia 77; irritability 66; headache 50; pain in legs 46; vomiting 44; backache 28; urinary retention 16; sore throat 9; diarrhea 4; pain in arms 4; bronchitis 4, and restlessness 3.

Gordon¹⁵ noted the first symptom in 100 cases to have been fever in 38; pain 38; headache 37; vomiting 17; diarrhea 11; urinary retention 9; coryza, constipation and convulsions each 6, and drowsiness 2.

Wilson¹⁶ noted that in 400 cases the symptoms and signs in order of their frequency were fever 398, being the initial sign in 334 cases; drowsiness 288; stiffness of neck 161; constipation 156; irritability 153; pain 130; tremor 113; headache 78; vomiting 67; muscular twitching 64; sweating 45; retraction of head and flexion of lower extremities 40; cough 38; injected fauces 31; red throat 27; skin lesions 27; diarrhea 25; abdominal pain 25; sore throat 21; urinary disturbance, usually retention, 21; convulsions 6, 2 of which had had previous convulsions.

Frauenthal and Manning¹⁷ quote Shepherd's figures of fever 198; pain and tenderness 184; headache 100; retraction of neck 79; sore throat 59; apathy 24; delirium 19; rigid neck 18; irritability 13; restlessness 11; unconsciousness 11; twitching 5; convulsions 4. The frequency of unconsciousness and de-

lirium and the infrequency of restlessness and irritability are noteworthy.

La Fétra and Schwarz, noting the frequency of signs and symptoms at the onset and in the early stage of the disease, observed fever in 684 of 745 cases; restlessness in 369; apathy in 294; vomiting in 25 per cent of the cases; headache 162; rigidity of the neck 121; constipation 107; diarrhea 103; stupor 71; delirium 62; skin eruptions 61; convulsions 51; coryza 45; sore throat 45; photophobia 26; Kernig's sign 19; bronchitis 19.

Weisenburg's¹⁸ figures on 710 cases seemed to be valuable only in relation to certain phenomena which we may feel sure he has carefully analyzed. It is important to note that of 710 cases only 3 patients had urinary retention and only 9 had convulsions.

This general survey indicates the symptoms and signs commonly observed. Some characteristics of these may be elicited from comparison of their descriptions.

Fever.—All authors are agreed that fever is the most constant sign and often the first sign of the onset of this disease. Onset with chill is quite rare. The fever may be of such short duration as to be overlooked (Ruhräh¹⁹). The temperature ranges between 101 and 103 F., rarely going as high as 104 or 105 F. It is maintained for a few days, usually disappearing within a few days after paralysis occurs, although in some cases it may continue for weeks into the period of convalescence, La Fétra and Schwarz noting fever lasting over seven days in 111 of 745 cases. It falls gradually without oscillations or by crisis. Wickman has observed a second rise of temperature with increase of paralysis. Weisenburg states that he has never observed a case with or without rise of temperature in which paralysis became more marked once improvement had begun. Slight morning remissions may be noted.

Fischer²⁰ calls attention to severe cases in which a sudden rise of temperature occurs, lasts forty-eight hours and falls by crisis. Such sudden rises have been taken for sunstroke (Frauenthal and Manning). The so-called "toxic" cases show

a longer febrile period. Intercurrent infections, abscesses, otitis media, gastro-enteritis and superficial infections may be responsible for sudden rises of temperature in the course of the disease (Weisenburg). In certain cases remissions of fever may last for two to six days.

The pulse rate is proportionate to the temperature and is not markedly accelerated except in severe cases, although Aycock notes it as being disproportionately rapid to the temperature.

In children old enough to locate it, pain is frequently an overshadowing feature of the disease. At other times it is trifling. It may appear as headache, which may be occipital and of a severe throbbing character. It may be frontal, severe and persistent. Pain may occur in the neck, along the spine, down the legs to the heels and soles, in the extremities, chiefly the legs, and in the abdomen. According to La Fétra and Schwarz it is very frequently present at the back of the knees and calves. In certain instances when the pain and tenderness have been disproportionately great, some cases have been classified as neuritic, but Collier²⁷ points out that this type is only some variety of the spinal type with a great deal of pain. It often resembles rheumatism, but the deep reflexes in ordinary painful states are invariably increased throughout the course of the disease. Occasionally the pain is most excessive in an extremity which later becomes paralyzed. The pain commonly is diffuse and continuous. At times the diffuse character of the pain has suggested influenza, but Ruhräh says that severe pain should speak against such a diagnosis. When the pain occurs in the abdomen it may be so severe that appendicitis may be diagnosed (LeBoutillier²⁸). Often the pain is more severe at night. Weisenburg in his series found that the pain came on after paralysis in most adults, lasted a week or two, or would at times disappear suddenly. At times the pain shortly preceded the paralysis.

Hyperesthesia and tenderness are often included with pain in the description of the symptomatology. Hyperesthesia was present in 75 per cent of the Hesse Nassau cases. In some

cases there is hyperesthesia to the slightest touch, in others tenderness to pressure and manipulation to the muscles. Armstrong noted no case of hyperesthesia of the skin. Wickman, however, noted many cases in which the slightest touch was painful, at times mere approach to the bed gave rise to anxiety and protest, and the patients were unable to tolerate the contact of bed clothes. More frequently, however, tenderness to pressure over muscles and tendons, and at times nerve trunks as well as to manipulation of joints has been present. Tenderness may last from two to three weeks, rarely to several months. Sensitiveness of spinous processes may be noted.

Where spontaneous pain has been absent, pain could be produced by passive movements, especially of the vertebral column, particularly ante flexion of the spine, and attempts to evoke Kernig's sign. The pain elicited by ante flexion of the cervical spine induces resistance and gives rise to what has been termed the "spine sign" by Draper, which was found by Armstrong in 82 per cent of cases and lasted several days. Stiffness of the neck is found in the majority of cases in some series. At times this rigidity is semivoluntary, less frequently it is completely involuntary and rarely opisthotonos is seen. Aycock says, "The patient tilts the head on the neck but does not bend the neck on the shoulders. As a result, the head can be brought about half way upward, when resistance is encountered and the child complains of pain." More constant and characteristic is the stiffness of the back. The patient is unable to sit up and bend the head on the knees. If they bend at all, it is at the hips, the spine being held rigidly. Ante flexion of the spine may produce pain in the lumbar region. In contrast to the rigidity of the neck to ante flexion, Ruhräh calls attention to backward falling of the head when the patient is raised by placing the hands under the shoulder. "If the child is told to raise the head when it is sufficiently conscious, it will hold it forward a moment or so and the head will again fall back." He considers this as a sign of great importance in the meningeal form of this disease.

A true Kernig sign is rarely present except in the meningeal cases.

Foerster²¹ called attention to reflex hypertension of the vertebral column which he frequently observed on attempting to raise recumbent children. Occasionally a scaphoid abdomen was seen.

The sensorium and behavior of the patient may be affected very early and at times lassitude and drowsiness are the first symptoms. The patient is apathetic and wants to sleep all the time. The apathy may result in a stuporous condition, rarely with typhoidal appearance. Some patients are extraordinarily irritable and fretful when aroused, complaining, at times excited. Others are extremely restless, wide awake, with hyperactive mentality. The drowsiness may last from two or three days to a week. A tendency to delirium is seen at times, hysterical laughing or crying has been noted and the presence of confusion. Coma rarely occurs except in lethal cases. Delirium may accompany high fever. At times maniacal outbursts have been recorded, and at times delusions.

The child often tosses about from side to side, not lying in one position more than a few minutes, sitting up, standing up, with the head turning in a perfectly purposeless way (Ruhräh). Often the child lies on the back without making an effort to move, the face showing apprehension. Often only the eyes are moved and not the head, the child being acutely attentive to all that goes on. A froglike position with slight flexion and eversion of the legs may be seen. A peculiar tired, wilted expression with a drowsy almost sleepy condition from which the patient may be roused by manipulation is noted by Peabody, Draper and Dochez.²²

The first signs may be those common to all illness in children, a change in disposition, disinclination to play, irritability, crying at night, grinding of the teeth, peevishness, dissatisfaction and crossness.

Muscular twitching, tremor and jerky movements are seen in 20 to 40 per cent of the cases. Muscular twitching was observed in only 31 of 100 cases reported by Armstrong, in 20 of 90 cases reported by Fraser, and 64 of 400 reported by Wilson who found 113 cases of tremor in the same series. The tremor

occurs at times in single muscles or groups of muscles of the extremities, often preceding the paralysis by twenty-four to forty-eight hours. At times the tremor resembles an intentional one. At times the tremor could only be demonstrated when the fingers were outstretched (Heiman²³). Walshe described the tremor as a jerky one, appearing when the patient is handled or makes voluntary movements. Zingher²⁴ found both fine and coarse tremors, especially in the fingers and hand or in entire extremities. Colliver²⁵ in a small series called especial attention to the tremulous condition and peculiar twitching, tremulous, convulsive movement of certain groups of muscles, lasting a fraction of a second to a minute or so, elicited by stroking the skin with the finger, by movement of the bed clothes over the sensitive skin, or by effort of the patient to coordinate. He noted it twelve hours to three days before paralysis, increasing as point of paralysis approached. Fischer likewise considered this of great value. Draper attributes great importance to the appearance of ataxic tremor and twitching, which he feels represents the early intoxication of the anterior horn cells and precedes the paralysis. At times the extremity being the most tremulous is the one to be paralyzed.

Convulsions are unusual. Many older authors described the twitching in the extremities as convulsions. At times they have been described as being only tonic and not associated with loss of consciousness. Wilson reported 6 in 400 cases and of these, 2 had previous convulsions. In 710 cases Weisenburg observed only 9 with convulsions, 3 being seen in hemiplegic encephalitic form. He says it is also noteworthy that many cases admitted during the epidemic with a history of convulsions proved, on further study, to be some type of meningitis. La Fétra and Schwarz observed 51 cases with convulsions in 745 cases, a rather high percentage.

E. Müller and Wickman have called attention to an initial increase in the deep reflexes in the preparalytic stage. The increase may extend into the paralytic stage most often in those in whom paralysis is slight, or in the legs when only the arms are involved, or in those in whom spastic paralysis is seen as

the result of pyramidal tract involvement and in meningitic cases. Weisenburg likewise noted exaggerated deep reflexes, as do many others. Regan²⁶ and Armstrong noted their diminution just preceding paralysis.

This is the usual observation and even persistence of a deep reflex during the paralytic stage is rare indeed. When found, it indicates a rapid recovery (Collier²⁷) or involvement of the pyramidal tract. Ankle clonus is indeed rare, although it has been noted early by Foerster, Weisenburg and others. Regan said it was often simulated in painful cases, which is likewise true of the false Kernig sign. The plantar reflexes are exaggerated in the preparalytic stage, accompanied by withdrawal of the entire leg. A Babinski sign has been noted in the preparalytic stage and usually indicates a meningitic form of the disease. Disturbances in bladder function are rare but a certain number of cases are always observed. Usually retention is observed for a short time, ordinarily not exceeding forty-eight hours. Armstrong noted 16 cases in a series of 100, Gordon 9 in 100, Wilson 21 in 400. La Fétra and Schwarz noted it only once in 684 cases.

We have been dealing chiefly with the signs and symptoms due to possible involvement of the subarachnoid space and the nervous system. Often the disease is ushered in by disturbances elsewhere. At times gastro-intestinal disturbances are prominent. Anorexia is the rule. Vomiting may be present and may be so marked as to suggest an acidosis (Ruhräh). It may last for several days. Constipation is the rule in some epidemics, diarrhea in others. At times the diarrhea with a fetid greenish stool suggests an acute gastro-intestinal catarrh (Wickman). The vomiting and constipation which may be exceedingly obstinate may lead to a suspicion of an intestinal obstruction (LeBoutillier²⁸). The tongue is tremulous, coated yellowish-white, or the edges red and the papillae pronounced. Later a "war map" character may appear (Carr²⁹). Regan³⁰ says that the edges and tip of the tongue are devoid of covering, a slightly deeper red. The papillae are not deeply colored or greatly enlarged. He likewise called attention to an absence of coating

in areas where normal membrane may be seen, giving a "geographical" outline.

In some epidemics the disease is ushered in by symptoms involving the respiratory tract. Müller reported coryza, sore throat, conjunctivitis, severe bronchitis, or occasionally bronchopneumonia in half of his cases. Neustaedter³¹ considered "the paleness of the nasopharyngeal mucosa and its edema, accompanied in the early stage by a serous and frothy transudate as constant and pathognomonic of the earliest prodromal stage." Sheffield³² said that the "tonsils presenting either simple congestion or also small grayish-white deposits when associated with palatal palsy may suggest diphtheria." Regan, in a communication describing the throat manifestations, found congestion an almost constant symptom during the early stage of the disease, never intense, involving the faucial mucous membrane, the base of the palate, pillars of the fauces and uvula; the soft palate is of a purplish, violaceous tinge. "It is this tinge which is distinctive." Inasmuch as the hard palate remains a pinkish-blue normal color there may be three zones of color; deep red faucial mucous membrane, red mixed, purple of the soft palate and pinkish-blue of the hard palate. He found a mild inflammation of the tonsils, which were enlarged with pronounced crypts. Rarely was there an exudation from the mucous membranes. A gingivitis was present in 10 per cent of cases. Epistaxis was common in the epidemics of Cornwall and of one in Wisconsin.

Skin manifestations occur in varying numbers in different epidemics.

Sweating has been noted as an important early sign by Müller, Krause and Starr. Müller found it in 75 per cent of his cases. Peabody, Draper and Dochez found it in only 25 per cent of their cases. Ruhräh said it "may be as marked as the colliquative sweats seen in typhoid." Sometimes it is limited to one part of the body, as the face or neck, or to one half of the face or an extremity. Wilson reported profuse sweating, out of proportion to the fever present in 45 out of 100 cases. Armstrong in 240 cases did not find it to be marked. In many epidemics it is entirely absent.

Pallor about the lips and nose often is observed.

In the New York epidemic of 1907 cutaneous eruptions were found in 61 cases. Peabody, Draper and Dochez did not see any eruptions in 183 cases. Regan found 114 rashes in 1017 cases, appearing on the second day or as late as the fifth to sixth week; 80 per cent of them occurred in the first week and lasted an average of four days. They occurred on the chest, cheeks, back, abdomen, less on the arms and legs. The meningitic type was more frequently associated with a rash, which might be papular, papular scarlatiniform, papulomacular scarlatiniform, or resemble miliaria. Herpes were notable by their absence but Müller found 3 cases of herpes labialis in 100 cases. Desquamation is rarely mentioned, Römer seeing it in one case, but Regan observed it fairly often. It rarely involves the palm and soles and may persist for three to four weeks. In some cases Collier has seen large, black-purple papules over a paralyzed extremity. Alternating blushing and paling of the skin in small spots or over large areas, at times quite transient, has been described by Ruhrah.

Carr found the superficial lymph nodes enlarged in 90 per cent of cases, the posterior cervicals being the most prominent, which is of some importance in relation to Burrows' conception of the disease.

Although Müller reports a leukopenia occurring, subsequent observers all report a leukocytosis. In the New York epidemic a leukocytosis of from 13,400 to 20,600 was found and this has been found to be true by most authors. It is usually highest in the lethal cases.

The above-described signs and symptoms may lead to a presumptive diagnosis of poliomyelitis and an examination of the cerebrospinal fluid often is the chief aid in the diagnosis of the preparalytic stage. It is not always an aid and at certain times may be normal. Draper points to the change occurring only after the stage of general invasion and the latent period have passed. This indicates the necessity for repeated examinations in suspected cases. However, Schless stated, "The mechanical irritation produced in frequent entrances into the

spinal canal, as advocated by Draper, might very readily produce increase in fluid pressure and in globulin, and in cell counts up to as small a number as 50 per cubic millimeter." It may be possible that a slight increase in cells does actually occur as the result of this procedure but the subsequent more marked changes which may be found before paralysis, frequently offer indubitable diagnostic aid.

The volume is seemingly increased. At times the pressure is increased. The fluid is clear in direct light but when viewed by transmitted light in a dark room a "ground glass" appearance may be seen, as pointed out by Zingher. A small fibrin web may form, though this is not as large as in tuberculous meningitis, and readily breaks up into small flakes. The albumin and the globulin are increased. There is a pleocytosis, usually between 50 and 250, but occasionally as high as 750, rarely 1000. In many series a pleocytosis has been constant but on the other hand in 34 cases reported by the Harvard Commission and found not to be pleocytosis, a cell count below 15 was found. The cells are generally mononuclears, but when examined very early there is, as Lyon³³ has pointed out, 50 per cent of polynucleated cells. When in the course of twenty-four to thirty-six hours there is a shift to a mononucleosis of 90 per cent or more, this he considers pathognomonic of poliomyelitis. Neal,³⁴ on the other hand, believes the polymorphonucleosis represents a special type of the disease and is very rare. Large mononuclears and endothelial cells are more frequent than in other conditions. Fehling's solution is always reduced. The Lange gold sol test shows a change in the luetic and meningitic zones in a considerable portion of cases, as pointed out by a number of observers.

The increased globulin may be seen in the third week and may persist after the return of a normal cell count.

Rarely a bloody fluid has been seen and at times a yellowish, spontaneously coagulating fluid. The chlorides are normal.

Zingher stated that when the fluid is shaken, a much denser, finer, more voluminous or persistent foam is seen than in normal fluids.

The duration of the above-described preparalytic stage varies. Usually paralysis occurs within two to three days. It may last as long as twenty-one days, very rarely. Armstrong notes it in 70 per cent by the third day and in 95 per cent by the fifth day. Paralysis is often ushered in suddenly, but may be immediately preceded by a weakness which may be demonstrated only by the patient being unable to bear his weight. When permitted to attempt to walk, some patients show an ataxia. The initial paralysis, as observed in the majority of cases, proved to be the final extent. Spiller³⁵ felt that the paralysis, preceded by weakness, required several days for its full development but rarely was it progressive over more than two weeks. Wickman said it was very seldom complete at the beginning, usually increasing rapidly in extent and severity. Collier has noted of these spreading cases that when the paralysis has remained the same for a number of hours, it spreads no more. In any case, once improvement begins, there is no further increase of paralysis. After reaching its height the paralysis begins to recede. As a rule, the distal muscles recover first, the upper before the lower extremity.

The type of paralysis is characteristic. It is a flaccid one, with atony, loss of deep reflexes, and is followed by muscle atrophy. After the tenth day, reaction of degeneration is found. Very rarely is an increased deep reflex found in a paralyzed extremity except in spastic paralysis due to cerebral involvement and myelitis above the bend of the reflex arc examined. The superficial reflexes likewise disappear, although Wickman has found conserved abdominal reflexes when the abdominal muscles were paralyzed. Weisenburg said he has never found this to be true. When observed, the Babinski sign is usually due to meningeal involvement.

Absence of deep reflexes is the rule. They may be normal in the bulbar cases. When only one leg is paralyzed the other knee jerk may be normal, and if only the arms are paralyzed the knee jerks may at times be present, rarely exaggerated. Even if only the facial muscles are paralyzed, the knee jerks may be absent.

One of the characteristics of the paralysis is its bizarre and unsystematic distribution. It picks out predominately the peroneal, quadriceps and deltoid muscles. Many fantastic combinations are seen, as right shoulder and left leg; both thighs, both legs and left forearm; both arms, the face and left thigh; both thighs and left leg; the external rectus and a leg. The lower extremities are affected much more than the upper. The paralysis is rarely complete in an extremity; the proximal muscles are more frequently affected. When a certain group of muscles is severely paralyzed, the adjacent ones may be little affected.

At times, especially in infants and young children, it may be difficult to discover the paralysis. Although able to move their extremities about in bed, the patients may be unable to stand. Passive movement is unresisted by the toneless muscles, and the force of gravity is not resisted by the paralyzed when occasion arises. When the lower extremity is passively flexed, for example, and suddenly released, it falls into a position of abduction or slides into an extended position. Plantar stimulation, slight pricking with a pin or tickling is not followed by withdrawal, or certain muscle groups are not seen to contract when others do.

Sensory changes are rare and fleeting. Transverse lesions may produce them but the etiology of such rare cases is controversial.

Bladder disturbances are rare and of short duration, and disturbance of rectal function, with the exception of constipation, is very rare. Only once incontinence of feces was observed by Weisenburg.

Among the cases diagnosed inaccurately as poliomyelitis are found tuberculous meningitis, mumps meningitis, rheumatic fever, diphtheritic palatal palsy, rickets, infectious diarrhea (Silverman,³⁶ Aycock). Of 37 cases wrongly diagnosed, Weisenburg noted 10 cases of cerebrospinal meningitis, 6 of tuberculous meningitis, 6 of pneumonia, 2 of otitis media with meningitis, 2 scurvy, 1 scarlet fever, 1 neuritis, and 4 with no diagnosis. Of 64 cases reported to the Harvard Infantile Com-

mission with wrong diagnoses, there were cases of infectious diarrhea, gastro-enteritis, influenza, vaccination, hysteria, tuberculosis, digestive upsets, nervousness, epidemic meningitis, luetic meningitis and tuberculous meningitis.

From a number of sources the following diseases are obtained as at times simulating poliomyelitis. In the preparalytic stage the exanthematous diseases, as measles and scarlet fever; tonsillitis, diphtheria, croup, influenza, bronchopneumonia, gastro-enteritis, appendicitis, enterocolitis, typhoid fever, intussusception, ptomaine poisoning, nephritis with uremia, eclampsia, rheumatism, scurvy, dentition, trichinosis, acidosis, tetanus, rabies, the meningitides and meningismus, chorea, lethargic encephalitis, and subarachnoid hemorrhage.

In the paralytic stage at times a differential diagnosis must be made from the pseudoparalysis of scurvy, hysteria, injuries and disease of joints, especially tuberculosis, cerebral arterial thrombosis, sinus thrombosis, amaurotic family idiocy, the cerebral palsies of childhood, polioencephalitis, disseminated encephalomyelitis, cerebral tumor, abscess, transverse myelitis, hematomyelia, syringomyelia, Friedreich's ataxia, Pott's disease, traumatic paralysis, spina bifida occulta, progressive muscular atrophy, muscular dystrophy, infectious neuronitis, multiple neuritis, Bell's palsy, birth palsy, diphtheritic palatal palsy, and myatonia congenita.

This formidable list suggests that if one were to describe the differential diagnosis of poliomyelitis it would be necessary to write several books on neurology, medicine and pediatrics. However, although it is conceivable that the several diseases mentioned in relation to the preparalytic stage of the disease must be differentiated, many of those concerned with the paralytic stage are related more to the residuals of the disease than its early form. The task, therefore, is materially simplified.

During an epidemic and in the months of July, August and September, an illness ushered in by fever, headache, pains, gastro-intestinal, respiratory or anginal symptoms should give rise to a suspicion of poliomyelitis. As pointed out by Ruhräh, in such an illness when signs of involvement of the central ner-

vous system are found, the diagnosis is liable to be poliomyelitis. This is true with the exception of diseases presenting meningismus and certain other inflammatory diseases of the nervous system, as meningitis, encephalitis, infectious neuronitis and some others.

In the preparalytic stage, the cases ushered in by signs of gastro-intestinal involvement with vomiting or diarrhea, among others may be suffering from the following diseases. Typhoid fever may usually be differentiated by its long prodromal period, the characteristic fever chart, the slow pulse with high fever, the leukopenia, differing from the American epidemics, enlargement of the spleen, the rose spots, blood cultures rarely, the early positive Widal reaction and, if examination found necessary, a negative spinal fluid.

The diarrheal diseases of infants and children, because of the frequency of nervous system symptoms and meningismus, are frequently very difficult to diagnose. The less severe types have a short duration and are quickly relieved by simple measures. The more severe types usually are accompanied by high fever, often bloody stools and the gastro-intestinal symptoms overshadow the nervous ones. Vomiting is more pronounced. The spinal fluid is negative. The vomiting, prostration, collapse, retracted abdomen and rapid stupor of cholera infantum differ from the ordinary picture of poliomyelitis. Intussusception is afebrile with tenesmus, marked prostration and acute pain with later abdominal signs, tumor, tympanitis, reversed peristalsis.

In cyclic vomiting, usually a history of many previous attacks will be obtained. The presence of acidosis is shown by acetone, diacetic, and oxybutyric acid in the urine. The vomiting is more severe, more frequent and the exhaustion more marked.

Of the diseases affecting the respiratory tract the following may be mentioned. Although enlarged tonsils are frequently seen in poliomyelitis, the appearance of the throat in poliomyelitis as described differs from the disease. There is painful cervical adenopathy frequently associated with a rigid

neck, retracted head and disinclination of the patient to permit its movement. The temperature is often higher and chills frequent. Diphtheria followed by palatal palsy is differentiated by the typical appearance and positive cultures of the Klebs-Löffler bacillus.

Where generalized pain is present, influenza may be difficult to differentiate. Leukopenia is common during the acute stage, although a normal or slightly elevated count may be seen in the mildest cases. The signs of involvement of the respiratory tract are more marked and are compatible with the general symptoms. The pains are aching, generalized, usually not so severe, not associated with the hyperesthesias, or limited to any extremity. The epidemics are not likely to occur in summer and spinal fluid examination is negative. In scurvy not only is the pain and hyperesthesia confusing, but a pseudoparalysis may lead to some difficulty in diagnosis. The hemorrhagic gums, subperiosteal hemorrhages, epiphyseal separations, ecchymoses, and excessive tenderness are characteristic.

Rheumatism rarely affects children under two years. In older children it runs a subacute and chronic course; arthritis is less extensive and more transitory. There is a history of relapses or of pleurisy, carditis, chorea, subcutaneous nodules. In the adult the evidence of characteristic joint involvement and cardiac disturbance and negative spinal fluid differentiates the disease.

Early in the course of tetanus, the rigid neck, stiffness of the arms and legs, headache and slight fever may give rise to a picture similar to meningeal types of preparalytic poliomyelitis. The history of an injury is of paramount importance. When trismus appears and a generalized rigidity of muscles, as well as the convulsions precipitated by stimuli of noise, jarring, etc., of course the diagnosis is apparent. Before this time the spinal fluid is free from globulin and has no increase of cells.

Nephritis with convulsions and uremia with convulsions are differentiated by the urinary findings of casts and albumin, and the evidences in the blood of nitrogen retention, high creatinine content, etc.

Early in the summer of 1894, Dr. Charles S. Caverly noticed that an acute nervous disease, which was almost invariably attended by some paralysis, was epidemic in Rutland County, Vt. Dr. A. Jacobi, from written descriptions of the epidemic, pronounced it one of cerebrospinal meningitis. Drs. M. Allen Starr and Charles A. Dana then decided it was anterior poliomyelitis. Although at that time little was known of the differential diagnosis, even now the differential diagnosis of preparalytic poliomyelitis and some other infections of the nervous system is difficult.

Of these infections leptomeningitis in any form is the most common. This is as true of the preparalytic stage as of the so-called "meningeal" form of the disease. Here meningeal symptoms occupy the foreground. Headache, vomiting, pain in the neck, Kernig's sign, opisthotonos, convulsions, somnolence or unconsciousness are present. In many only an ocular palsy may be the residual.

In meningismus common to many infectious diseases, there is usually no increase of albumin or globulin, or it is very slight. There may be a slight increase of cells up to 20 to 50. The Lange gold sol reaction is negative. Often the removal of spinal fluid is followed by long-lasting relief of symptoms and signs. It may be found to be associated with some other known disease sufficiently characteristic to make the diagnosis. At times it may be impossible at any one stage to differentiate it in the absence of an epidemic. At times the absence of tremor, ataxia, twitching, pain and tenderness are of assistance. The cerebrospinal fluid examination differentiates the meningitides from poliomyelitis. In tuberculous meningitis the frequent xanthochromia, marked fibrin web, pellicle formation, spontaneous coagulation, characteristic absence of a reducing (Fehling's) substance, marked increase of globulin and albumin, longer lasting period of polynucleosis in the acute stage, the finding of the tubercle bacillus, and low chlorides are characteristic.

In pyogenic cerebrospinal meningitis, a turbid fluid, the decrease in Fehling's reduction, greater increase of protein, positive culture of meningococcus or other infecting organism, the

discovery of the organism in the fluid by staining, and a high cell count with predominant polymorphonuclears are found.

In luetic meningitis a clear fluid with slight increase in protein, negative culture, positive Wassermann reaction, low cell count, and a more marked Lange curve in the luetic zone are seen.

In tuberculous meningitis a history of infection with tuberculosis in the patient or family may be obtained. The onset is slower, evidence of tuberculosis elsewhere may be found, rarely the finding of choroidal tubercles, the predominance of cerebral signs at times associated with hydrocephalus and evidence of increased intracranial pressure with papillitis, more marked mental symptoms, marked Kernig and Brudzinski signs, and markedly retracted neck serve to differentiate the condition.

Epidemic cerebrospinal meningitis occurs most frequently during epidemics, the evidence of meningitic involvement is much greater, with Kernig and Brudzinski signs, opisthotonos, the typical capillary hemorrhagic rash, with marked leukocytosis, slow pulse, the common occurrence of herpes labialis, at times positive blood culture, and absence of gastro-intestinal symptoms with the exception of vomiting characterizes the condition.

Septic meningitis is usually secondary to a focus in the middle ear, accessory nasal sinuses, scalp or face. The course is extremely rapid and the cerebrospinal fluid quickly becomes purulent and the responsible organism is readily found.

The occurrence of encephalic types during epidemics of poliomyelitis has led to the separation of this group. The coincidence of lesions in the anterior gray matter with spastic paralysis seems to indicate the propriety of such classification, despite the controversial character of the literature.

Some of the other encephalitides offer difficulty in differential diagnosis when occurring sporadically. Particularly is this true of some of the cases of supposed serous encephalitis in which the general symptoms are indistinguishable. Marked fluctuation of the signs, such as paresis, aphasia, occasional optic neuritis, rapid disappearance of signs after spinal punc-

ture, and absence of all signs pointing to involvement of the spinal cord or its meninges, is at times sufficient to make a diagnosis. Pyogenic encephalitis or early abscess may imitate the onset of poliomyelitis. The history of acute recent otitis, accessory nasal sinus disease, more marked mental symptoms, greater incidence of convulsions, particularly of jacksonian type, the slowly progressive evidence of intracerebral involvement, absence of spinal cord involvement, signs of increased intradural tension with slow pulse and occasional optic neuritis, higher leukocytosis and deeper clouding of consciousness are suggestive.

Epidemic encephalitis when sporadic may, because of its protean characteristics, offer considerable difficulty. In the spinal fluid an increased sugar content is distinctive. When pain is common, myoclonic jerking, especially of the abdominal wall, is characteristic. The predilection for the midbrain, the peculiar somnolence, especially catalepsy, and increase of signs of progressive involvement over a longer period of time are evidences against poliomyelitis. At times the anterior roots may be involved, producing similar reflex and motor disturbance to that seen in poliomyelitis. The predominance of cerebral signs again may lead to a proper diagnosis.

Acute disseminated encephalomyelitis, because of the multiplicity of lesions, frequent involvement of the brain stem, nystagmus, evidence of pyramidal tract involvement, long-lasting bladder disturbance, is more readily differentiated.

At times the symptoms of a brain tumor in a child may appear suddenly with headache or vomiting. The exclusive involvement of intracerebral contents, evidence of increased intracranial tension, with slow pulse and papilledema, perhaps a secondary hydrocephalus, absence of fever or leukocytosis, and generalized pain distinguish the condition.

Marantic venous sinus thrombosis is associated with greater stupor, is usually afebrile, convulsive seizures are more common, signs of bilateral cerebral involvement are present in bizarre combinations.

Pyogenic venous sinus thrombosis is ushered in with a chill,

the temperature rises as in septicemia and blood cultures are positive.

Some diseases, because of simulation of paralysis, must be excluded during the early paralytic stage. Rickets, scurvy, osteomyelitis, hip joint disease, osteochondritis syphilitica and chorea are among such diseases.

In general it may be said that in contrast to the general hyperesthesia and pain in poliomyelitis in these diseases the pain or tenderness is limited to certain joints rather than extremities. The characteristic bony changes in rickets, the symmetrical involvement, carpopedal spasms, laryngismus stridulus and changes in response to electrical stimulation are characteristic.

In tuberculosis of joints, which at times has been confused with poliomyelitis, and poliomyelitis with hip joint disease, there is immobility of joints because of pain and not because of a paralysis or paresis. The limitation of movement is characteristic, limited in certain directions, as in hip joint disease, to flexion, abduction and external rotation of the thigh. The onset is insidious; much longer continued fever and emaciation, and local joint changes are demonstrable.

When paralysis has occurred, multiple neuritis must be differentiated. The onset is usually much slower, the paralysis is gradually progressive over weeks before its height has been reached, the distal parts are involved more than the proximal, the fever lasts longer, the pains are of longer duration and at times more severe. Sensory disturbances are more common and severe. Usually combinations of cranial nerve palsies with symmetrical peripheral paralysis speaks for multiple neuritis. The distribution of the paralysis is peripheral, not segmental in type.

Postdiphtheritic paralysis may appear painlessly. It is always symmetrical. At times a history of preceding sore throat may be obtained, at times not. Palatal palsy and paralysis of accommodation of the sphincter of the iris may have been noted, positive throat cultures may be obtained, disturbance of deep sensibility is common with varying degrees of ataxia, and cardiac symptoms are common.

Infectious neuronitis often producing symptoms of a multiple neuritis, with bladder disturbance and segmental sensory or motor loss, develops more slowly, has a longer febrile course, is often symmetrical, combining the features of a multiple neuritis and cord disturbance at times involving the pyramidal tract.

Although a transverse myelitic form is described, in poliomyelitis it is very rare. In sporadic cases the differential diagnosis is based upon the evidences of involvement of the pyramidal tracts, the sensory disturbance, the lasting bladder and rectal disturbance. Early in its course the paralysis is flaccid and the deep reflexes absent, but it may even then be differentiated from that due to disturbance of the gray matter by the reflex withdrawal of an extremity upon plantar stimulation by deep scratching or pin prick, which proves the integrity of the lower motor neuron. The same is true of the cerebral palsies, when the paralyzed muscles may be flaccid. Other diseases producing transverse lesions of the cord may likewise be differentiated. Hematomyelia, in addition to the absence of fever and general symptoms, often shows dissociated sensory changes. In Pott's disease, when a paraplegia may at times be of sudden onset, a definite level of paralysis and sensory loss may be discovered, x-ray evidence of the diseases of the bone be found, and spinal puncture reveal evidence of a spinal fluid block.

In the preparalytic stage no single sign is pathognomonic of the disease. When viewed as a whole, particularly during an epidemic, the signs and symptoms are sufficiently characteristic to make a presumptive diagnosis and often the changes in the spinal fluid may make the diagnosis positive. This is by no means true of all cases. In the paralytic stage, with the exception of Landry's paralysis which is by many considered as a type of poliomyelitis and the rare transverse myelitic type, the diagnosis is more readily made, even in sporadic cases. It is possible that some immunological test other than the development of immune bodies will be discovered which will permit of certain diagnosis in the preparalytic stage, so that when adequate methods of treatment be developed, very early treatment may

be instituted to the end that the disease be aborted before paralysis occurs.

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visualization was just mentioned. Likewise in intrahepatic lesions where extensive liver damage has been done, *e. g.*, in portal cirrhosis with ascites, there is nonvisualization even though the extrahepatic system itself is functioning normally. This is in the patient who is not icteric. When the biliary excretory mechanism has been so altered by a pathologic process that the normal excretory product is regurgitated back into the blood stream, it is hardly to be expected that the foreign dye could be eliminated successfully. If the failure to excrete bile and its associated choluric syndrome is due to disease of the extrahepatic passages, it is obvious that visualization will not occur. However, in the case where jaundice results from an intrahepatic lesion whether visualization occurs or not will be determined by the amount of undamaged liver. If the functional reserve of the liver can compensate for the liver damage to a degree which will permit an adequate amount of dye to be excreted, then visualization may be expected to occur, provided that the ducts, the gallbladder and the sphincter of Oddi are functionally intact. Non-visualization in the presence of jaundice results from the same disturbances of the process of excretion as does the jaundice itself and these causes may be either intrahepatic, producing medical jaundice (infectious or regurgitation jaundice due to necrosis of liver cells (Rich)), or surgical jaundice (obstruction). The differentiation of these two types of jaundice often offers considerable diagnostic difficulties. They are usually distinguished from each other, clinically, by the history in the medical type of an upper respiratory infection, an epidemic, a dietary spree (mushrooms, chili con carne, an alcoholic excess, overripe fruit, etc.) or the taking of certain drugs (cinchophen, carbon tetrachloride, salvarsan), while in the surgical type there is the history of long-standing "biliousness" and "fat dyspepsia," previous attacks of colic or vague right upper quadrant pain. Then there are the associated symptoms of colic or pain preceding, coincidental to or succeeding the onset of jaundice which is more often present in the surgical case. The course of the jaundice, the development of a mass, the enlargement of the gallbladder, the size of the liver,

the development of a palpable spleen all help to decide to which group the individual case belongs. Frequently the clinical picture is so indistinct that the individual case defies classification. The view that this difficulty is real is supported by the number of tests which have been introduced to make this decision, particularly the van den Bergh, the galactose tolerance test, the study of urobilin, plasma cholesterol and cholesterol esters, etc., all of which have been found wanting, because of the variability of the results obtained. Most often the difficulty in diagnosis occurs in those cases in which the symptoms are of relatively recent onset and of moderate severity and it is usually the differentiation of an infectious jaundice from a mild obstructive jaundice due to a "silent stone."

Case I.—This man had been well until six weeks ago when he rather suddenly developed nausea and vomiting. This persisted during the night and was associated with frequent loose bowel movements. He had a cramplike pain in his upper abdomen which did not radiate and was not constant. These attacks of pain lasted for about two days but the nausea and vomiting still occur from time to time. Within two days after the onset he was icteric with light colored stools and dark reddish colored urine. Itching was troublesome and after the first few days constipation was marked. The bitter, metallic taste is annoying. A careful inquiry was made to elicit the presence of precipitating causes but there was no history of upper respiratory infection (by which about half the cases of catarrhal jaundice are preceded), he had taken no medicine, received no injections, had not been drinking and there was no dietary indiscretion. To establish the possible history of a gallbladder disease, he had had no previous attacks, was not addicted to the use of cathartics, had no "biliousness" or "fat dyspepsia." No predisposing factor for either group could be made out in his past history; he had the usual childhood illnesses but he had not had typhoid, malaria, lues or previous attacks of jaundice. His habits were not unusual. Again particular care was given to elicit facts which might be relevant but he was abstemious, he used alcohol only on rare occasions, he was not fond of and did not indulge in highly spiced foods, condiments or other dietary articles high in manganese content. He has lost 18 pounds since the onset.

Physical examination at the time of his admission ten days ago in the fifth week of his illness revealed a well-nourished, middle-aged man (aged forty-eight) of the hyperesthenic habitus with moderate icterus and evidences of pruritus as revealed by scratch marks. The liver was palpable two fingers below the costal margin, the edge was smooth, firm and not tender. The gallbladder could not be felt. Traube's space was tympanitic and the spleen could not be palpated. The abdomen was relaxed and, while it was liberally covered with fat, lent itself well to examination, and no masses, tenderness, rigidity or fluid could be discovered. No other significant findings were present.

Laboratory Examination.—The urine was deep amber in color and contained bile, the stool clay colored, and contained no blood. A series of stools examined with the mercuric chloride test gave a constantly positive result for stercobilin. The icterus index was 60 on admission to the hospital and a more recent one taken yesterday gave a reading of 63, indicating a constant level. The van den Bergh, of course, gave a direct positive reaction; the serum bilirubin measured 5.6 mg. per cent. The bromsulphalein test gave a retention of the dye in thirty minutes, graded as 3 plus. The galactose test showed an excretion of 2.8 Gm. of urinary reducing substances in five hours. The blood Kahn was negative. The Wallace and Diamond test showed urobilin concentration through a dilution of 1 to 60. There was a secondary anemia as shown by hemoglobin of 60 per cent and erythrocyte count 3,800,000. Ewald test meal showed free acid of 20 degrees, total of 45 with no blood.

The roentgenological examination of the gastro-intestinal tract was negative. The Graham-Cole test showed a good visualization of the gallbladder.

Diagnostic Considerations.—From the history no predisposing or etiologic clue is given. The onset of the jaundice with pain, while suggesting a surgical case, is more than overbalanced by the severity of the gastro-intestinal symptoms with vomiting and purging. The physical findings also are indefinite, the absence of splenic enlargement is of no positive help, though, if it were enlarged, this would be a very valuable sign of medical cause. The moderate intensity of the jaundice together with the bile in the stool, indicating an incomplete icterus and indefinite results of the urobilin test, could result from either cause. The maintenance of a constant bilirubin level in his seventh week with repeated attacks of vomiting, together with the results of the galactose test point toward an extrahepatic obstruction. The course, an unexplained jaundice of six weeks' duration with a persisting level, is ordinarily indication for an exploratory, if the condition of the patient permits. In this case the good visualization of the gallbladder, indicating as it does good function, definitely classifies this as a case of intrahepatic infectious jaundice.

Cholecystography in the presence of jaundice has not been widely used. There is a fairly definite impression that it is contraindicated because of possible potential danger—an idea undoubtedly inherited because of the earlier experiences with phenoltetrachlorophthalein which was somewhat toxic, in that it not infrequently produced severe general and local reactions. The general impression as to its value is tritely expressed by Eusterman³: "It is unfortunate that in cases of jaundice which so often give rise to difficulties in diagnosis, and in which it is so frequently desirable to determine the causative rôle of the gallbladder or its actual condition, cholecystography is contraindicated because the dye would be held back by the liver; at any rate a negative shadow would not be significant."

the development of a palpable spleen all help to decide to which group the individual case belongs. Frequently the clinical picture is so indistinct that the individual case defies classification. The view that this difficulty is real is supported by the number of tests which have been introduced to make this decision, particularly the van den Bergh, the galactose tolerance test, the study of urobilin, plasma cholesterol and cholesterol esters, etc., all of which have been found wanting, because of the variability of the results obtained. Most often the difficulty in diagnosis occurs in those cases in which the symptoms are of relatively recent onset and of moderate severity and it is usually the differentiation of an infectious jaundice from a mild obstructive jaundice due to a "silent stone."

Case I.—This man had been well until six weeks ago when he rather suddenly developed nausea and vomiting. This persisted during the night and was associated with frequent loose bowel movements. He had a cramplike pain in his upper abdomen which did not radiate and was not constant. These attacks of pain lasted for about two days but the nausea and vomiting still occur from time to time. Within two days after the onset he was icteric with light colored stools and dark reddish colored urine. Itching was troublesome and after the first few days constipation was marked. The bitter, metallic taste is annoying. A careful inquiry was made to elicit the presence of precipitating causes but there was no history of upper respiratory infection (by which about half the cases of catarrhal jaundice are preceded), he had taken no medicine, received no injections, had not been drinking and there was no dietary indiscretion. To establish the possible history of a gallbladder disease, he had had no previous attacks, was not addicted to the use of cathartics, had no "biliousness" or "fat dyspepsia." No predisposing factor for either group could be made out in his past history; he had the usual childhood illnesses but he had not had typhoid, malaria, lues or previous attacks of jaundice. His habits were not unusual. Again particular care was given to elicit facts which might be relevant but he was abstemious, he used alcohol only on rare occasions, he was not fond of and did not indulge in highly spiced foods, condiments or other dietary articles high in manganese content. He has lost 18 pounds since the onset.

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intrahepatic cause for the jaundice, while a negative shadow is of no significance.

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We have been accustomed to employ cholecystography in cases of choluric jaundice when the clinical evidence is indefinite with the understanding that an absent shadow on the cholecystogram is of no value either one way or the other; but a positive shadow in the presence of jaundice indicates a normal function of the extrahepatic bile passages and hence the disease state must be intrahepatic. Rudisill,⁴ with intravenous administration of the dye, obtained visualization in 7 of a series of 8 cases of infectious (catarrhal) jaundice. At the Cook County and Research and Educational Hospitals there were found 29 cases of jaundice in which visualization had been attempted. Of these, 16 were medical and 13 were surgical. Visualization after the oral administration of the dye occurred in 11, or 68 per cent, and of these in 8, or 50 per cent, the shadow on the cholecystogram was good. In the 13 surgical cases comprising common duct stone, carcinoma of the common duct and head of the pancreas, no shadow was obtained in 100 per cent. In only one of the medical cases was the dye given intravenously and in this one neither the gallbladder shadow nor the homogeneous bowel shadow described by Delario⁵ was seen.

The degree of jaundice as measured by the icterus index ranged from a minimum of 30 to a maximum of 112 in the medical group with visualization occurring in one instance with a degree of jaundice graded 90. The average for the group was 58. In the surgical cases the jaundice was more intense as evidenced by the fact that the average for the group was 73.

In no instance was any note made of unusual reactions or any untoward effects, nor of any increase in symptoms following the administration of the dye.

In two of the medical cases the clinical evidence was so indefinite that even in spite of the good visualization it was felt that an exploratory was indicated and in both of these no extrahepatic pathology was found.

Hence, we feel that the visualization of the gallbladder in the presence of jaundice is indicated in a limited number of obscure cases and that the development of a shadow means an

as though by a specific cytotoxic agent with rapid and complete dissolution of the hepatic parenchymata as in acute yellow atrophy, yellow fever and infectious jaundice.

After making allowances for individual peculiarities, the pathologic changes which occur within the liver as a result of toxic processes in general tend to be fairly uniform. A typical sequence of events occurs. First, liver cell damage as expressed by cloudy swelling, fatty degeneration, necrosis and hemorrhage, occurs with consequent disruption of the liver cell cords and the clinical manifestations of toxic jaundice. Second, connective tissue replacement, both within and without the lobules, ascribed to the activity of the stellate cells of v. Kupffer, may occur concomitantly or follow the parenchymatous damage. Apparently the mode of deposit of connective tissue follows no definite rule; ultimately, however, with the progress of the connective tissue replacement, the parenchymatous hepatic cells gradually become divorced from the portal vascular system, the portal blood ultimately finding its way back to the general circulation by devious channels.

Coincident with parenchymatous damage, hemorrhage and connective tissue replacement, regeneration of liver cells may progress at an amazing speed. This was known to Virchow in 1847, who spoke of the process as regeneration of bile capillaries. However, the true significance of this process has only recently been appreciated. Experimentally, Whipple has demonstrated the prodigious ability of the liver cells of dogs to regenerate under favorable conditions, and he has estimated that, if one can apply the findings in experimental work on dogs to man, under the same conditions an animal the size of man should regenerate over 100 Gm. of liver cells per day. By liver resection experiments Mann has come to a similar conclusion, namely, that a dog may regenerate six sevenths of the mass of liver cells in six weeks.

It would seem that the ability of the parenchymatous liver cells to regenerate after liver injury is a protective mechanism comparable to conservation processes not uncommonly seen in lower forms of animal life. It is true that the uniform archi-

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CINCHOPHEN POISONING

FROM a biological point of view the liver may be considered a mass of undifferentiated cells which is chiefly concerned with processes of nutrition. It contains no highly differentiated tissue comparable to that of other parenchymatous organs and its multiplicity of functional activity is in marked contrast to the apparent simplicity of the architecture of the hepatic lobule. The cuboidal hepatic cells and the "fixed-wandering" cells of v. Kupffer are the essential functioning element of this mass.

The parenchyma of the liver is constantly undergoing change in unison with many physiologic and pathologic processes. It is concerned with the absorption, transformation and storage of carbohydrates, proteins and fats. It is a reservoir for water and blood storage. It is as a mass peculiarly sensitive to injury by a variety of toxic substances. Cloudy swelling, fatty degeneration and necrosis of hepatic cells may result. The degree of involvement apparently depends not only upon the specific sensitivity of the liver cells to such toxic substances but also upon the intensity and duration of the intoxication. Curiously enough certain segments of the liver cell cords may be particularly affected—those about the central vein as in chloroform poisoning and anoxemia; those at the periphery of the lobule as in eclampsia; and the central zone in infectious diseases, whereas the effect of some poisons such as phosphorus and cinchophen may be more uniformly distributed within the hepatic lobule. The intensity of the process may vary greatly; the whole mass of liver cells may, in fact, be profoundly affected

estimated that one twentieth of the liver cell mass is sufficient to carry on normal liver function. In addition, the remarkable ability of the liver parenchyma to regenerate new and functionally active liver cells contributes materially toward the so-called "silence" or "functional reserve" characteristic of the liver. The clinician must be constantly on guard in estimating the amount of liver damage that may actually be present in a given patient, even though the patient may be entirely free from symptoms.

Of first importance in the management of patients with parenchymatous liver damage is the recognition and elimination of the hepatotoxic agent. This is not always easy or possible. However, the physician should always be suspicious of drugs, by whatever name, recently taken, and of alcohol and recent infections. When possible, all such should be eliminated.

Based on experimental and clinical observations, the insuring of an adequate water intake, the administration of easily assimilable carbohydrate food or glucose in adequate amounts, the limitation of proteins to a maintenance level, the avoidance of fats and finally, with the recognition of impending or manifest cirrhosis of the liver, the adoption of a diuretic regimen calculated to circumvent ascites should be adopted. Glucose is usually well tolerated. Three hundred to 500 cc. of a 25 per cent solution of corn syrup in fruit juice may be administered several times a day by mouth or nasal tube. Glucose is irritating and not readily absorbed by the colon and should, therefore, not be administered in enemas. Glucose in 10 per cent solution subcutaneously or intravenously slowly administered may be given if need be. In the acutely toxic patient glucose intravenously should not be withheld even for a few hours.

Experience has shown the wisdom of continuing patients with suspected hepatic disease on a high carbohydrate diet for a long period of time. Such a diet affords the maximum known factor which contributes toward restitution of damaged livers to a normal functional status.

Two patients recently studied in this clinic serve well to illustrate many of the features of hepatic disease which have

texture of the liver lobule is lost in the process of regeneration, but fortunately it is equally true that the liver cell cords thus regenerated possess the ability of carrying on liver functional ability.

Whipple has shown that regeneration of liver cells does not occur during starvation, in the presence of common duct obstruction or in the absence of adequate flow of blood through the portal system. However, in the absence of these adverse conditions regeneration of liver cells occurs at a rapid rate when the experimental animal is maintained on a diet rich in carbohydrate.

Clinically, advantage should be taken of the protection against liver cell injury afforded by a high carbohydrate diet and the consequent maintenance of a substantial glycogen content within the liver at all times.

The management of patients with parenchymatous damage of the liver should take into consideration the characteristic reactions which occur within the liver cell mass which have been outlined above. It should be noted that liver cell damage may be functionally balanced by liver cell regeneration, and connective tissue deposit may be functionally balanced by the establishment of an adequate compensatory circulation. In fact at any stage of the sequence of events a functional balance may be established. In this connection the clinician should appreciate the importance of the time element involved. A few hours may mean much in fortifying the liver cells against what appears to be an almost specific cytotoxic process, as in cinchophen, phosphorus and chloroform poisoning. On the other hand, it may never be too late to establish a functional balance in patients with cirrhosis of the liver, the result of connective tissue deposit within the liver occasioned by a variety of toxic agents and in those who have threatened or manifest toxic jaundice or ascites.

Curiously enough, the pathologic sequence of events outlined above may progress to a high degree of development and remain nonsymptomatic. Obviously this is due to the remarkable functional reserve possessed by the liver. Mann has

weeks' duration. On two occasions she vomited fluid containing bile. She had been constipated for years and addicted to the daily use of cathartics. No other history of gastro-intestinal disturbance. For a month prior to the onset of the symptoms she had taken cinchophen in unknown quantities for arthritis of her knees, back and shoulders, present since April, 1931. Past history included five normal pregnancies and exophthalmic goiter in 1925 from which she made a spontaneous recovery. She was acutely ill, obviously from toxic jaundice; temperature 98.6 F., pulse 110, blood pressure 162/100. There was a slight but definite exophthalmos. Both the pharynx and nasopharynx were

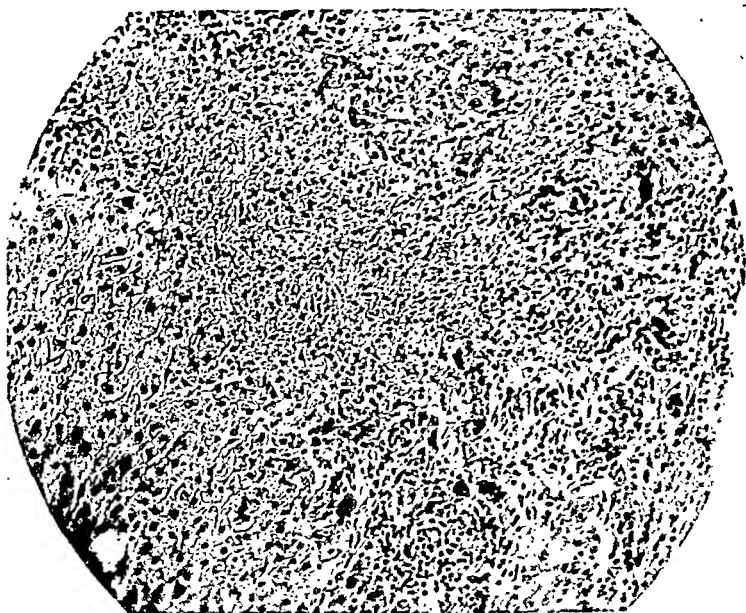


Fig. 82.—Microphotograph of a portion of the liver showing but little hemorrhage. The hepatic cells are enormously swollen, there is a great increase in the number and irregularity of the liver cell cords (bile ducts?), of which many contain deposits of pigmented material and there is marked connective tissue replacement throughout.

injected and pus was expressed from both tonsils. Thyroid was not palpable, lungs clear. A systolic blow was heard over the entire precordium with maximum intensity over the mitral area. Abdomen distended with gas and ascites and tender throughout. Liver not palpable.

Blood count showed red blood cells 4,540,000, white blood cells 6600 and hemoglobin 65 per cent (Newcomer). Smear was normal. Stools were clay colored with no urobilin or blood present. Urine intensely jaundiced, specific gravity 1.018, albumin present, a few granular casts. Van den Bergh direct promptly negative; indirect to 13.9 mg.; icterus index 116; blood sugar 88; blood urea nitrogen 17.1 mg.

been mentioned above. In both instances the patients have taken a drug, cinchophen, in relatively small amounts as a remedy to combat "rheumatic" pains. One patient died at the end of three months after having taken an unknown amount of cinchophen for one month. Two and one-half grains of cinchophen to be taken three times a day had been prescribed by a physician living at a distance. The autopsy findings in this case are presented.

The second patient recovered. He had received a total of 180 grains of cinchophen administered over a period of six days.

Case I.—Mrs. J. B., aged fifty-two, entered Passavant Memorial Hospital on September 12, 1932. She had noted progressive jaundice, pains in the right



Fig. 81.—Anteroposterior section of the liver showing extensive hemorrhage and massive areas of regeneration of liver cell cords. The size of the liver is greatly reduced; 9 x 12 cm. in this section.

hypochondrium upon taking food or fluids, abdominal distention, dark stools, dark-colored urine, and a papulomacular rash over the body.

he stated that he had been treated for sacro-iliac pain following a year of frequent colds and "lowered resistance." He was placed in a hip cast for six weeks and given cinchophen, one 7.5-grain tablet four times daily, or a total of 180 grains over six days. In August he developed a nonspecific prostatitis for which he was treated by a urologist. On September 17, 1932, a tonsillectomy was performed under local anesthesia following which a hemorrhage occurred which was controlled only by pressure and hemostat. Other history unimportant. On entrance he appeared acutely ill; weight 154 pounds (70.4 Kg.); temperature 98.6 F., pulse 80, blood pressure 96/70. There was no evidence of oral infection. The lungs and heart appeared normal. The abdomen was slightly distended with gas and tender throughout with some acute tenderness in the region of the liver which could not be palpated. The area of liver dullness was diminished.

Blood count showed red blood cells 5,000,000, white blood cells 9300, hemoglobin 80 per cent (Newcomer). Smear was normal. Urine showed much bile; albumin 2 plus, some red blood cells and an occasional granular cast. The stools were light tan in color and contained urobilin. Bromsulphthalein showed 70 per cent retention at the end of five minutes and 30 per cent at the end of thirty minutes. Van den Bergh direct promptly positive, indirect 13.9 mg.; icterus index 12; cholesterol 725; blood Wassermann negative.

He was placed on a high carbohydrate diet which he tolerated well, along with 250 Gm. of glucose and as much as 400 Gm. of hard candy by mouth daily. After ten days of treatment the liver tenderness disappeared, the edge being palpable a handbreadth below the costal arch. All symptoms except the icterus disappeared. He was discharged on November 28, 1932, with a slight icterus, at which time he weighed 164 pounds (74.5 Kg.). On three occasions while in the hospital the fat and protein content of his diet was increased with a rapid return of symptoms. On January 10, 1933, he was entirely free of jaundice and weighed 176 pounds (80 Kg.). His liver appeared normal in size. At this time he was taking a normal diet.

Diagnosis.—Parenchymatous hepatitis due to cinchophen poisoning.

Comments Concerning Cinchophen. — Cinchophen, phenyl-quinoline-carboxylic acid, was first introduced as a therapeutic agent in 1908 when Nicholaier and Dohrn¹ observed increased excretion of uric acid following its administration and suggested its possible value in the treatment of gout. The first preparation of this drug appeared under the name of atophan. An editorial which appeared in the Journal of the American Medical Association, August 2, 1930, states: "Its striking effect on the elimination of uric acid captured the clinical imagination which was at that time perhaps somewhat overconscious of uric acid." The drug did appear to have specific action in cases of acute gout but its action on tophi seems to be very limited; how-

The patient was given glucose and fluids by all possible means with no apparent benefit. She became stuporous, delirious, and died in coma on September 15, 1932.

At autopsy the abdomen was found to contain approximately 1500 cc. of bile-stained fluid. The liver (Figs. 81-83) weighed 540 Gm. The capsule was thickened but not wrinkled; the surface was yellow-brown, mottled with red dots. Cut surface showed an increased amount of blood with numerous yellow nodules separated by dark red hemorrhagic areas. The liver cut with increased resistance.

Microscopical Examination of Liver Tissue.—A large proportion of the liver tissue is absent and its place is partially filled with blood. Between these regions

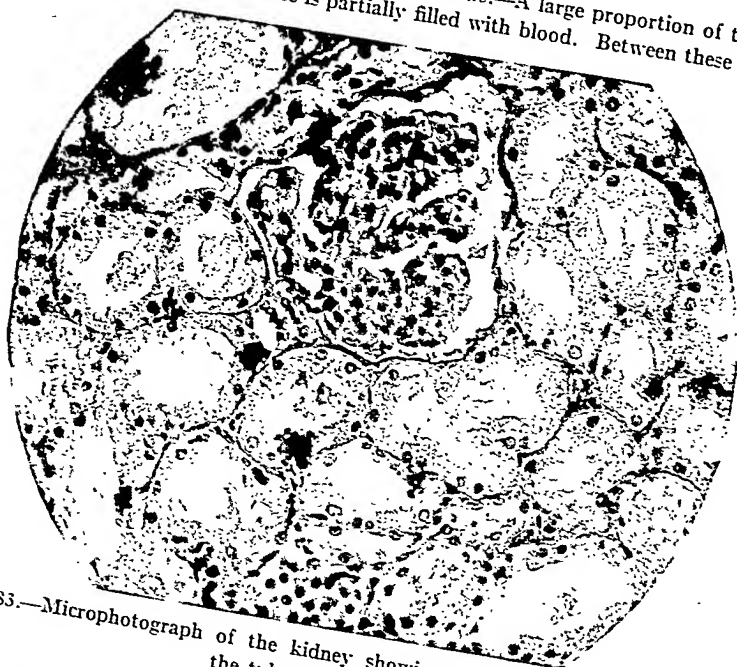


Fig. 83.—Microphotograph of the kidney showing extensive degeneration of the tubular epithelium.

the bile ducts appear increased in number and the tissue between them is infiltrated with lymphocytes and polymorphonuclear leukocytes. Cells of the remaining liver tissue are enormously swollen, the cytoplasm is foamy and the sinusoids are almost obliterated. Many bile capillaries are filled with plugs of yellow-brown material.

Diagnosis.—Subacute yellow atrophy of the liver due to cinchophen poisoning.

Case II.—Mr. W. R., aged forty-one, lawyer, entered Passavant Memorial Hospital on October 10, 1932, with complaints of progressive fatigue, nausea, anorexia, loss of 7 pounds in body weight, and painless jaundice of sixteen days' duration, which had its onset with fever and chills. Three months previously

Cinchophen is well tolerated by the majority of individuals to whom it is given. This is substantiated by its extensive use at the present time, the *relatively* few deaths reported from its use, by the fact that atophan was used clinically five years before any untoward effects resulting from its use were reported in the literature, and that another ten years of its use passed before a fatal case of acute yellow atrophy was definitely associated with poisoning by this drug. The first ill effects to be reported from its use were cutaneous, later gastro-intestinal, and finally the more insidious parenchymatous liver damage. Gargill⁴ has classified the many forms of cinchophen intoxications as follows:

1. Cutaneous manifestations such as pruritus, angioneurotic edema, urticaria, macular and papular rashes as first reported by Phillips in 1913.⁵

2. Anaphylactoid reactions characterized by neurocirculatory disturbances associated with rapid pulse and lowered blood pressure as described by Scully⁶ in 1924.

3. Gastro-intestinal disturbances including simple ulcers of the mouth, pyrosis, nausea, vomiting and diarrhea reported by Schroeder⁷ in 1922.

4. Parenchymatous liver damage as indicated by toxic jaundice first noted by Worster-Drought⁸ in 1923.

Since the first reports of liver damage resulting from cinchophen poisoning have appeared, the literature has contained numerous articles describing deaths from acute yellow atrophy following the use of this drug. Most of these articles have included a single case, few with two, and an occasional article with three or more. Among these may be mentioned Cabot,⁹ who first demonstrated the gross pathology of cinchophen poisoning, Sutton,¹⁰ Lowenthal, Mackay and Lowe,¹¹ and McVicar and Weir.¹² Rabinowitz¹³ reported 7 cases from one hospital and listed 43 others collected from the literature. During the past year more cases have been reported than in any previous year. Of the more than 100 cases reported the mortality rate is over 50 per cent. The number of unreported cases probably is very large.

ever, its analgesic properties, quite similar to those of the salicylates, became well known and it was because of these properties that many indications were found for its use.

Atophan was well known in this country prior to the World War but no cinchophen preparations were manufactured in the United States until imports from Germany were stopped. Since that time the use of cinchophen has increased tremendously; it has been used as an analgesic in all forms of myalgia, neuralgia, arthralgia and kindred distresses, for which salicylates were previously administered.

With cinchophen preparations coming into general use and with acceptable cinchophen products being manufactured in this country, there have appeared so many available products containing cinchophen that it is difficult to classify or even identify them. Preparations such as atophan, nov-atophan, phenylcinchoninic acid, cinchosal, cincho-vess, mono-iodo-cinchophen, atophan-urotropin, cinchopyrene, atophynol and cinchodine suggest in their names the presence of atophan or cinchophen, whereas agotan, quinophan, phenoquin, faranstan, biloptin, weldona and numerous patent rheumatic "cures" give no indications of the presence of the drug either by name or by label. It is regrettable that such widespread and promiscuous use of this drug has occurred and that too few realize its toxic properties and the hazards of its use.

"The U. S. Pharmacopeia, IX, described the product under the name acidium phenylcinchonicum (phenyl cinchoninic acid). Later the Chemical Foundation and the Council of Pharmacy and Chemistry adopted the coined, non-proprietary name 'cinchophen' under which name it is described in the recently issued edition of the Pharmacopeia (U. S. P., X)."²

Although the drug under the name of "atophan" was found no longer acceptable in New and Non-official Remedies and was excluded in 1921, cinchophen and cinchophen derivatives are still listed as "useful in acute gout" and "when proper doses are given, *generally* without undesirable effects."³ The dosage suggested in gout is from 0.5 Gm. ($7\frac{1}{2}$ grains) four times a day to 1 Gm. (15 grains) three times a day.

poisoning are confined for the most part to the liver. Hemorrhages into the gastric mucosa and ulcers of the mucosa and serosa of the stomach and cloudy swelling and fatty degeneration of other parenchymatous organs may be considered as part of the general intoxication.

Beaver and Robertson¹⁶ have made a detailed study in 5 fatal cases and report that the lesions found in cinchophen poisoning resemble, if not exactly duplicate, those found in acute and subacute yellow atrophy and in toxic cirrhosis of the liver produced by other causes. The outstanding characteristics, as reported by these writers, are: (1) Relatively rapid necrosis and autolysis of the hepatic parenchyma resulting in atrophy of the liver; (2) relative increase of connective tissue without injury or proliferative reaction on the part of the connective tissue framework or vascular apparatus of the liver; (3) predicted on the duration of life following the initial atrophy, regeneration of hepatic parenchyma from existent parts spared by the initial destruction will ensue; this degeneration is extremely irregular and patchy and may occur as large nodules.

Conclusions.—In view of the dangers incident to the administration of cinchophen, the unknown susceptibility of individuals to its toxic effects and the length of time which may pass after its administration before toxic manifestations may appear, it seems unwise to administer cinchophen as a therapeutic agent under any circumstances, especially since many harmless and equally effective analgesic drugs are readily available for use.

The frequency and abandon with which cinchophen, a dangerous drug, is employed in the manufacture of proprietary and other preparations should be a matter of great concern to the medical profession as it is a menace to the public.

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Extreme tolerance to cinchophen by some individuals is well illustrated in Hensch's¹³ case. This patient is reported to have taken from 2.5 to 6 Gm. (40 to 90 grains) daily for a period of eighteen years for relief of arthritis. Intolerance to the drug in some instances is dramatically illustrated by a case reported by Lind¹⁴ where a total of 6 Gm. (90 grains) taken over a period of a few days following the extraction of a tooth very promptly produced jaundice which was followed by death from acute yellow atrophy in a few days.

The range of tolerance remains unexplained. Probably several factors are involved. Rabinowitz enumerates many conditions which he believes may predispose to intolerance to cinchophen, such as lowered glycogen content of the liver resulting from malnutrition, infections, hyperthyroidism, surgical operations with enforced starvation, as well as previous hepatic or renal damage. Constitutional or allergic hypersusceptibility are considered predisposing factors by others. Impurity of the drug itself may be another. Willcox¹⁵ believes that the specific toxic principle is the quinoline nucleus. He compares this action to that of arsenical compounds in producing liver damage. Sollmann¹⁷ suggests that the toxicity of cinchophen depends upon the incompleteness or oxidation of the quinoline nucleus in which highly toxic nitro compounds are created.

The earliest signs of intoxication may vary in character and intensity. Malaise, anorexia, nausea, vomiting, diarrhea, urticaria, vasomotor symptoms, a rash or a tender liver may appear before jaundice, or painless jaundice may be the first symptom. The subsequent course is that of toxic jaundice in general. Recovery is usually slow with persistence of the jaundice of some grade for a long period. A history of the use of cinchophen in any form, the use of an unknown medicine or a "rheumatic cure" for arthritis, or the taking of a medicine given for any condition for which such drugs are commonly used along with appearance of jaundice with or without other symptoms, justifies the suspicion that you are dealing with cinchophen poisoning.

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Fig. 84.—Lupus vulgaris.



Fig. 85.—Lupus vulgaris.

CLINIC OF DR. EDWARD A. OLIVER

RUSH MEDICAL COLLEGE

TUBERCULOSIS OF THE SKIN

You have seen several cases of tuberculosis of the skin recently and I should like to devote the remainder of our period here to a brief consideration of the subject of tuberculosis of the skin, including the tuberculides.

Tuberculosis of the skin was formerly considered a rather uncommon disease in this country as compared with its incidence on the Continent and in Great Britain. We are now seeing it more and more frequently. Whether the disease is really on the increase or whether our ability to recognize it is improving, I do not know.

The manifestations of this disease are almost as multiform as those of syphilis.

The four types of true tuberculosis of the skin are lupus vulgaris, tuberculosis verrucosa cutis, scrofuloderma and tuberculosis cutis orificialis.

Lupus vulgaris (Figs. 84-86) is not a common condition in this country. It is very common in Europe but whether because of our better living conditions or an inherent resistance in us, we do not have it in such large numbers as they do in Europe. The disease generally begins in early childhood. The primary lesion is a small nodule deeply imbedded in the skin. It is a pinhead- to pea-sized brownish-red or yellowish-red nodule. It is smooth on its surface and grows very slowly. When pressed with a glass slide or diascope a typical apple-jelly-brown color is apparent. The papule gradually increases in size until it becomes the size of a split pea. New papules appear and by coalescence a small patch is formed. The most common site for their development is the face on the cheek or

especially when it commences in adult life. Another not infrequent site is about the inner canthus of the eye. It rarely affects the scalp. The next most common locations are the backs of the hands, lobes of the ears, arms, legs and buttocks. It is seldom seen on the trunk. The amount of destruction that it causes depends a great deal on the patient's resistance. The disease generally begins in childhood, though we occasionally see cases that have begun in early adult life.

The disease is a slowly progressive one and one that taxes our patience and our ingenuity to properly treat.

Tuberculosis cutis verrucosa is, as the name implies, a warty form of tuberculosis (Fig. 87). We may see it in small

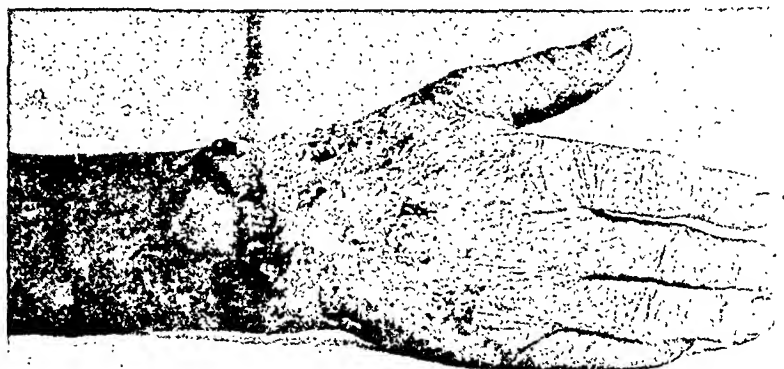


Fig. 87.—*Tuberculosis cutis verrucosa*.

plaques or in wartlike lesions. It is seen in those who perform autopsies or whose work entails the handling of cadavers, though many instances of its having been caused in other ways have been recorded.

The anatomical tubercle, or postmortem wart, is a thick hyperkeratotic lesion occurring generally on the dorsal aspect of the finger, evidenced as an indurated, pigmented lesion which may become fissured.

The ordinary plaque of verrucous tuberculosis looks not unlike a patch of blastomycetic dermatitis. It is seen most often on the dorsal surface of the hand or forearm. The lesion is

about the nose. The disease may and often does originate in the mucous membrane of the nose. In about 72 per cent of the cases the mucous membrane is involved sooner or later.

A typical patch of lupus vulgaris is clearly demarcated, barely elevated above the level of the skin, reddish-brown in color, soft to the touch, and smooth or covered with a fine scale. When pressed with a diascope, the apple-jelly-brown color of the



Fig. 86.—Lupus vulgaris.

individual nodules is easily seen. The center of the patch may undergo retrogressive changes and become ulcerated, crusted and on healing transformed into an uneven cicatrix, atrophic in one case, fibrous and keloidal in another, frequently presenting brownish-red foci of disease distributed through it. These patches spread slowly, taking years to produce the involvement of the skin that syphilis may in the same number of months.

In a large number of cases it begins about the nasal orifice,

Lupus miliaris disseminatus was first described by Tilbury Fox under the name, "disseminated follicular lupus." Since the lesions show no relation to the follicles of the skin, this name was discarded. This affection is a true tuberculosis of the skin. The lesions (Figs. 89-91) consist of flattened or slightly elevated, pinhead- to bird-shot-sized papules, round or oval in shape, at first bright red in color, later fading to a



Fig. 88.—Scrofuloderma healed.

brownish-red. These lesions appear in crops and are most often seen on the face, on the labial mucosa and occasionally on the nasal mucosa. Often an acute hyperemia precedes the outbreak, the lesions becoming manifest after the redness has subsided. They are soft to the touch and can easily be curetted out of the skin. The individual papules may persist for a long time, finally to shrink and disappear.

generally single, oval or circular in shape, definitely circumscribed, in size about that of a silver dollar to half dollar, brownish-red in color and covered with fine, dry, pointed vegetations. Both of these types are the result of the inoculation of the tubercle bacillus into the skin.

The lesions of *scrofuloderma* are produced by the tubercle bacillus as the result of extension from some underlying focus of tuberculosis. This type of lesion is seen most commonly on the sides of the neck from tuberculosis of the glands of the neck and in the skin overlying tuberculous bones and joints.

The most common lesions are ulcers which are linear and oval, the edges of which are undermined and ragged and the floors of which are covered with unhealthy granulations which secrete a watery purulent discharge. These lesions result from the gradual enlargement of tuberculous foci, such as glands in the neck, which, as they enlarge, become softer and attach themselves to the skin. The overlying skin becomes purplish-red, thinned and finally breaks down. Fistulous tracts often result, as well as these ulcerations.

The scars produced after these ulcers heal are corded and fibrous (Fig. 88), and in them may be found nodules or *scrofulous gummata*.

We might also mention here *scrofulous gummata*, a condition known as *tuberculosis colliquativa*. This condition, seen most often in children, occurs on the back and consists of deep-seated nodules of tuberculous tissue which tend to enlarge, break down and produce ulcers, just as occurs in the *gummata* in syphilis.

Tuberculosis cutis orificialis is the name given to tuberculous ulcers which occur most commonly about the lips, in the mouth and about the nose in patients suffering with pulmonary and laryngeal tuberculosis; about the anal region in intestinal tuberculosis; and about the glans penis and external genitalia in those afflicted with genito-urinary tuberculosis. These ulcers are generally oval or circular, shallow, painful and covered with thin crusts. They are most often seen in those who are in the last stages of tuberculosis.

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Papules capped with small pustules and crusts have often been seen and may at times be mistaken for acne or the lesions of papular syphilis.

There may be slight itching or no subjective sensations. This eruption may accompany other signs of visceral tuberculosis or it may appear in individuals who show no other signs of tuberculosis.

Miliary tuberculosis of the skin may follow exanthematous fevers in children. This, however, is a rare form, and appears



Fig. 89.—Lupus miliaris disseminatus.

as an acute generalized eruption of indolent, brownish-red, acuminate papules which may become necrotic and form minute ulcers.

Inoculation tuberculosis is another interesting type, differing from ordinary verrucous tuberculosis in that the regional lymphatics and glands are affected. A flat apple-jelly nodule appearing in the cutis or subcutaneous fat is the primary lesion. This nodule may be almost inconspicuous and located far from

namely, that these eruptions are due to the actual presence of the bacillus. Since the bacillus must be supposed to be destroyed when it reaches the skin, it follows that its demonstration in the lesions could only be possible in the very early stages. This Kyrle succeeded in doing. He had opportunity to observe a case of sarcoid in its very earliest stages. He was able to study microscopical sections of this lesion from its very earliest appearance until it reached the nodular stage. When the lesion was ten days old he demonstrated the tubercle bacillus in the section but in a study of the lesion on the twenty-first day and for many days afterward he never again was able to do it. Jadassohn's hypothesis was, therefore, substantiated by this and it also serves to explain the difference between the acneform tuberculide and multiple lupus.

Multiple lupus occurs in early childhood, usually after an attack of measles. The eruption is a profuse and widespread one of small papules, some of which eventually disappear while others remain and subsequently develop into typical patches of lupus which persist unless removed by treatment for the rest of the patient's life.

Acneform tuberculides occur not only in childhood but in older children and adults. They are not associated with measles or any of the exanthemata. The lesions do not persist for long and they do not increase in size. They may recur, however, time and again.

This contrast between multiple lupus and the acneform tuberculide is explained by the fact that during and after an attack of measles in a tuberculous subject there is a state of anergy or loss of resistance toward the tubercle bacillus, so that bacilli entering the blood stream from a tuberculous focus are not destroyed at once but remain active in the tissues in which they were deposited. In the case of the acneform tuberculide there is a state of allergy and the bacilli are destroyed by an active immunity reaction before they can multiply locally.

Lichen scrofulosorum, another one of the tuberculides, is generally seen in young subjects between the periods of infancy and puberty, rarely after the twentieth year. The lesions

bacillus in these lesions and for the tendency of them to undergo spontaneous involution, Hallopeau suggested that they were due to toxins from a tuberculous focus reaching the skin by the blood stream and there setting up an inflammatory reaction. Haury and Darier supposed them to be due to dead or attenuated bacilli which were able to cause an inflammatory reaction but not to multiply locally.



Fig. 91.—Lupus miliaris disseminatus.

It was not until 1913 that Jadassohn put forth a new hypothesis which now dominates our viewpoint. According to this hypothesis we need not suppose that the exciting agents of the tuberculides must necessarily be either toxins or dead and attenuated bacilli but that they may be living virile bacilli which are quickly destroyed in subjects who are hypersensitized by previous infection with tuberculosis. This is a theory which makes it difficult to prove one of its own essential features,

The usual lesions are pinhead- to pea-sized follicular papules or nodules which undergo necrosis and heal spontaneously with pitted scarring. These patients very seldom show any evidence of tuberculosis.

Erythema induratum (Fig. 92) is a chronic condition, tuberculous in the majority of cases, which involves the skin on the posterior aspects of the lower legs. It generally occurs in young women, especially those who are on their feet a great deal. The fact that this disease appears more frequently in the winter



Fig. 93.—Sarcoid of Boeck.

months gives support to the view that a poor peripheral circulation is a factor in its development. Many of these cases are seen in patients with cold, cyanotic hands and feet with a chilblain type of circulation.

The eruption consists of one or several deep-seated nodules, deeply situated in the skin of the calf of the leg. They are bluish-red in color, sometimes painful, and as they gradually extend to the surface the overlying skin becomes thinned and breaks down. The eruption is generally symmetrical and the ulcers produced are ragged, deep seated and heal very slowly.

are pinhead-sized and smaller papules, flat topped and rather firm. They are light red to a color approaching that of the normal skin. Occasionally they are surmounted by a fine scale. At first the eruption is discrete, later they tend to arrange themselves in coin-sized patches. The course of the disease is slow. In contrast to the acneform tuberculides, lichen

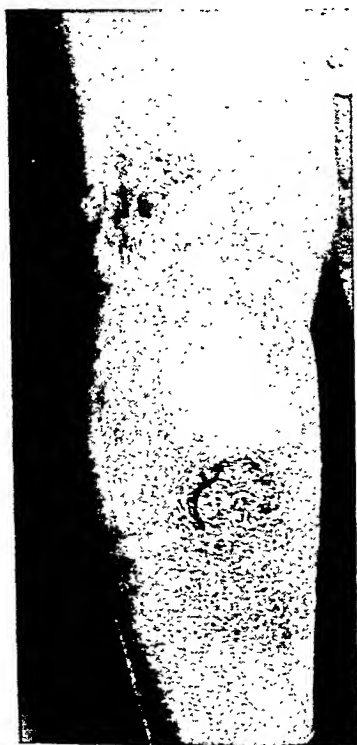


Fig. 92.—Erythema induratum.

scrofulosorum is frequently accompanied by enlarged cervical glands, scrofuloderma, enlarged mediastinal glands, bone tuberculosis, dactylitis, or even latent tuberculosis.

Papulonecrotic tuberculides appear in successive crops usually on the face, where the condition is known as acnitis, and on the extensor aspects of the extremities, where it is known as folliclis.

The bulk of evidence points to the fact that the tubercle bacillus is the causative agent of sarcoid. Histologically, practically all cases of this affection present a tuberculous or at least a tuberculoid structure, and as I previously pointed out, the reason why the tubercle bacillus is so difficult to demonstrate is because it dies rapidly and is only demonstrable in the very earliest lesions.

I am indebted to Dr. David V. Omens who photographed all but two of these patients at Rush Medical College.

Sarcoid.—The term "sarcoid" was first used by Kaposi to designate a group of diseases which were either sarcoma or resembled it very closely. This use of the term has now been discarded and the name applied to a group of affections characterized by the formation of indolent or diffuse infiltrations in the skin. The type originally described by Boeck (Fig. 93) occurs as nodules, papules and infiltrating plaques.



Fig. 94.—Sarcoid-like lesions in a patient with leprosy.

The color of the early lesions is red, later they become a dark brown. Under pressure these nodules are seen to be composed of grayish-yellow foci, which characteristic suggested the name of miliary lupoid. These lesions have only a limited growth and usually occur on the face, back of the shoulders and extensor aspects of the arm. They frequently heal under arsenical medication (Fig. 94).

REPORT OF CASES

Case I.—A housewife, aged twenty-four, had burning on urination, frequency and urgency. Previous cystoscopic examination, done by a competent urologist, had revealed bilateral pyelonephritis and cystitis. Her bladder had been irrigated with various solutions and medications, alkalis had been administered orally and yet the infection had persisted.

When the patient was first seen the urine was cloudy and was loaded with many pus cells; the stained sediment of the centrifugal specimen contained many gram-negative bacilli; the culture of the urine yielded many *Bacillus coli*.

At this time the administration of the ketogenic diet was begun. In five days the urine was clear and the patient's symptoms were considerably improved, although some pus cells were still present. In seven days the urine was still clear and in the urinary culture there was no growth from 0.1 cc. of urine. There was no frequency and no irritation. In twelve days the patient felt the best she had felt since the original infection started, the urine was clear, there were no pus cells and the culture was negative. The patient was then placed on a qualitative ketogenic diet which was continued for six weeks at home. After that period she was placed on an unrestricted diet for the next six weeks.

The patient was rechecked in three months and had no symptoms, urine was clear, there was no pus and culture was still negative 0.1.

TABLE I

(CASE 1)

Days on ketogenic diet.	Urine.	Diabetic acid test.	Pus graded 1 to 4.	Remarks.
1.....	Cloudy ++	0	++++	Culture of urine <i>B. coli</i> .
2.....	Cloudy ++	0	++++	
3.....	Cloudy +	+	+++	
4.....	Cloudy +	+	+++	
5.....	Clear	++	++	Symptoms improved.
6.....	Clear	+++	0	
7.....	Clear	++++	0	No growth on culture 0.1 cc. urine.
8.....		++++	0	
9.....		++++	0	
10.....		++++	0	
11.....		++++	0	No growth 2 cc. urine.
12.....	Clear	++++	0	
Qualitative ketogenic diet for six weeks....	Clear	+	0	No symptoms.
Placed on normal diet next six weeks.....	Clear	0	0	Culture of urine negative.

Case II.—A real estate man, aged forty-three, for thirteen months had recurring attacks of frequency, urgency, nocturia and burning at the end of urination. He was referred by a urologist who reported that his cystoscopic examination revealed a rather marked cystitis and severe prostatitis. He had been given repeated irrigations, prostatic massage, and many drugs. Culture of the urine revealed innumerable *Bacillus coli*. Phenolsulphonephthalein test was normal. Roentgenological examination was negative.

CLINIC OF DR. CLIFFORD J. BARBORKA

FROM THE DEPARTMENT OF MEDICINE, NORTHWESTERN
UNIVERSITY MEDICAL SCHOOL

DIETETIC TREATMENT OF CHRONIC URINARY INFECTIONS

IN reviewing the literature we find that many attempts have been made to free the urinary tract of the colon bacillus infection. Efforts to change the urine from alkaline to acid reaction and vice versa have been made with the hope that in the changed medium the growth of the organism would be inhibited. However, it is doubtful if the urine in such procedures ever is entirely free of the living organism.

From work done by Schohl and Janney, it is known that the colon bacillus is inhibited if the acidity or alkalinity of the urine is increased beyond a certain point (pH 4.6 to 5, acid, and at a pH 9.2 to 9.6, alkaline). The optimal growth of the bacilli takes place at pH 6 to 7; this is the average reaction of the urine of a person who is on a mixed diet. In a series of experiments on the relationship of the pH of the culture medium and the growth of the colon bacillus, it has been found that the urine may become free of organisms, as determined by culture, when the pH drops below about 5.6, probably because the urine is a highly buffered medium.

In searching still further for means of acidifying the urine and inhibiting the growth of the colon bacillus, I suggested the ketogenic diet. The purpose of this paper is to give a brief discussion of dietetic treatment of chronic urinary infections and to present the report of 2 cases of the chronic type of colon bacillus infection of the urinary tract who were treated by means of the ketogenic diet.

cases who were suffering from recurrent bacilluria of the *Bacillus coli* type. These cases were free from the bacteria and pus in the urine and in growth on culture within seven to thirty-five days from the beginning of the ketogenic diet. Helmholtz felt, because of his wide experience with former therapeutic results, that urinary infection in the presence of anomalies could not be cleared up by any form of medical treatment. Yet the first two cases of urinary infection with anomalies of the urinary tract, not benefited from any other procedure of therapy, were rapidly cured by means of the ketogenic diet. Hugh Cabot has discussed the treatment of infection of the urinary tract by the ketogenic diet and called attention to its possible value in the preparation of patients for operation on the urinary tract as well as in their postoperative treatment.

Helmholz has shown that acidity of the urine alone or in combination with diacetic acid apparently is not responsible for the bactericidal effect, but that some other substance or substances in the ketonurine from a properly administered ketogenic diet act antiseptically at a pH below 5.6. The importance of a low pH should be emphasized in applying the ketogenic diet to urinary infections, since it has been demonstrated that urine showing a strongly positive reaction for diacetic acid after using the diet is not bactericidal if the pH of the urine is 5.7 or above. There is a variability in the absorption and assimilation of a high intake of fat by different persons, as well as fluctuations in the degree of ketosis. Because of this fact, in cases when one cannot get the pH below 5.7, it may be necessary to combine with the ketogenic diet ammonium nitrate or ammonium chloride given orally to increase the acidity of the urine. The ketogenic diet can be planned so that the average patient will develop an intense ketosis in a few days and in most instances the pH will fall well below 5.6.

While the two cases reported obtained symptomatic relief quickly and the bactericidal effects occurred in from five to seven days, certain patients or conditions may require a longer period of time, probably from three to four weeks before beneficial results will be seen. Following the clearing of the urine,

He was placed on a ketogenic diet and in seven days was symptom-free; urine clear, no pyuria and culture negative. After the seventh day he was allowed to follow an unweighed qualitative ketogenic diet for three weeks. He has been on a normal diet now for six months without a recurrence at this time.

TABLE II

(CASE 2)

Days on ketogenic diet.	Urine.	Diacetic acid test.	Pus graded 1 to 4.	Remarks.
1.....	Cloudy +++	0	++++	Culture of urine B. coli.
2.....	Cloudy +++	0	++++	
3.....	Cloudy ++	++	++	
4.....	Clear +++	+++	+	Improved.
5.....	Clear +++	+++	Occasional	
6.....	Clear	+++	0	
7.....	Clear	+++	0	Symptom free, culture negative.
Qualitative ketogenic diet for three weeks.	Clear	+	0	Culture negative.
Normal diet for six months.....	Clear	0	0	Symptom-free.

DISCUSSION

The ketogenic diet consists of a large amount of fat, adequate amount of protein and a minimal amount of carbohydrate. When the ketogenic factors, or fatty acid derivatives of food, in the diet overbalance the antiketogenic factors, or glucose derivatives of food, ketone bodies (acetone, diacetic acid, and beta-oxybutyric acid) are formed as the intermediary products of the incomplete oxidation of fats. With the proper administration of the ketogenic diet ketonuria develops. The use of a few drops of a 10 per cent ferric chloride solution provides a simple means for the physician to test (diacetic acid test) the presence of these ketone bodies.

I would emphasize the fact that the ketogenic diet is not a cure-all; however, the results from its clinical application in the treatment of epilepsy and migraine for the past twelve years have been adequate to justify its classification among important new methods of treatment.

Since I first suggested the use of the ketogenic diet in urinary infections several reports have been made calling attention to the curative effect of the diet on infections of the urinary tract. A. L. Clark found and reported favorable results of

the disappearance of pyuria, and urine culture free from organisms, the patient may be allowed to change from a weighed quantitative diet to an unweighed qualitative diet for a few weeks. If after that time the patient is still controlled he may return to a normal diet.

Several factors should be mentioned in the consideration of the application of the ketogenic diet in chronic pyurias:

1. There is an apparent difference in the reaction of different organisms to this régime. Fortunately the *Bacillus coli* is the most common cause of urinary infection and it is the most sensitive to this treatment. The other gram-negative bacilli are more resistant, especially the *B. aerogenes*.

2. It has also been found that when there are marked renal lesions, the infected kidney not only will not put out a urine of low pH but it may interfere with the excretion of the acetone bodies.

3. For the present it would seem that the use of the ketogenic diet in urinary tract infections would best be applied in the treatment of chronic cases of pyuria, especially those having the *Bacillus coli* type of organism.

CONCLUSION

1. The ketogenic diet is a new and very promising method of treatment which has given marvelous results in chronic pyurias when carefully applied.

2. While it is essential for the patient to develop ketosis, the acidity of the urine must have a pH below 5.7 for the ketonurine to be bactericidal.

3. The fact that the ketogenic diet requires extra care and effort in its application may cause the treatment to be reserved for cases that have not responded to more convenient methods.

4. Adequate time has not elapsed to determine whether or not the clearing of a chronic infection of the urinary tract by means of the ketogenic diet is a permanent cure.

CASE REPORTS

Case I.—S. B. K., lawyer, aged sixty-six, was seen first at home February 3, 1927. In his past history he had typhoid fever at six; pneumonia at eighteen; tuberculosis with hemorrhages at thirty-three; fistula-in-ano at thirty-five; right retinal hemorrhage and a diagnosis of arteriosclerosis at fifty-one; visual disturbances accompanied by nausea at fifty-eight, lasting off and on for about one year, in the latter part of which vertigo seemed to replace the nausea. At age sixty, in 1925, he coughed bloody sputum at times.

My introduction to this patient was at 8.00 P. M., February 3, 1927, when the patient was in the midst of a severe acute pulmonary edema and appeared to be in extremis. This began at about 6.30 P. M. as an increasing dyspnea during his walk from the station to his home. He was observed sitting immobile in the orthopneic position, with ashy-gray cyanosis, dripping with sweat and with a heart rate of 144, respirations of 44 and a blood pressure of 220/155. His chest was full of coarse moist râles and he coughed large amounts of bloody sputum. On percussion the left heart extended 15 cm. from the midsternal line and the right, 10 cm. One hour later he was more comfortable and his blood pressure had dropped to 175/120, morphine and digitalis having been administered. By 10 P. M. I was able to leave. The next morning he was very comfortable with a temperature of 99.3 F., heart rate 120, respirations 24 and blood pressure 165/105. A bronchopneumonia supervened and pleural effusion developed. Later a paracentesis was done and 500 cc. of clear fluid was removed, which proved sterile. Electrocardiogram made on June 21, 1927 (Fig. 95, 1), showed left ventricular preponderance with myocardial damage and extrasystoles. His improvement was steady and he resumed his law practice, spending two summer months in France, from whence he returned in satisfactory condition. In October auricular fibrillation was first observed (FIB).

The year 1928 marked five periods of cardiac asthma (D), lacking the dramatic signs of acute pulmonary edema. It is reasonable to believe that they would have so terminated if they had not been met promptly. Electrocardiogram (Fig. 95, 2) made September 5, 1928, shows little change from Fig. 95, 1.

1929: This year included a moderate attack of cardiac asthma (D) in September and a more severe one in December, for which he was hospitalized. His urine showed a faint trace of albumin, no casts, and his phenolphthalein output was 42 per cent the first hour and 20 per cent in the second hour. The nonprotein nitrogen was 33 mg. Electrocardiogram (Fig. 95, 3) was made December 14, 1929, and showed a prolonged P-R interval and evidence of apparent increase in myocardial damage.

1930: A very satisfactory year, with occasional attacks of auricular fibrillation (Fig. 96) and his first attack of angina pectoris (ANG) May 21st. This year he gave himself more consideration and included many rest periods in his day's work. On October 29th he was seen with a marked Vincent's angina (V-ANG) and was hospitalized for a few days. The fusiform bacilli and spirillae rapidly disappeared under treatment. It is curious to note the rise in blood pressure at this time, since no cardiac factors seem to have been operative. One may deduce that the pain and discomfort affected vasomotor mechanism and caused the rise in pressure. From time to time the attacks of angina pectoris

CLINIC OF DR. VANCE RAWSON

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REPEATED ATTACKS OF ACUTE PULMONARY EDEMA COMPLICATING HYPERTENSIVE HEART DISEASE: A FIVE-YEAR STUDY OF TWO PATIENTS

THE clinical picture of acute pulmonary edema is one never to be forgotten—dramatic and terrifying because of the extreme dyspnea, bloody sputum, ashy cyanosis and profuse sweating, death seeming so imminent as to preclude beneficial therapeutic measures. Acute pulmonary edema occurring in elderly patients with arteriosclerosis, coronary sclerosis and myocardial degeneration is not infrequently observed, but repeated attacks are uncommon. The writer observed 2 such patients over a period of five years and visualized the blood pressure taken at each observation—over 200 readings in each patient. When these were graphed the occurrence of a marked rise in blood pressure during the attacks of acute pulmonary edema with a fall incident to relief of the myocardium, often within an hour, gave interest to the study. Also the fact that 2 patients showed such a marked similarity of events during the years between 1927 and 1932, consisting of a coronary occlusion, a persistent sensory aphasia ensuing on one of the attacks of acute pulmonary edema and a similarity of findings at autopsy, makes the record of the clinical histories worth presenting.

It is hoped that in correlating all of these events graphically we may arrive at a little better understanding of the processes involved, and that more observers may be stimulated to make notes and assemble them for study, so enabling us some day to know the cause of acute pulmonary edema and the attending phenomena.

recurred, responding promptly to the use of nitroglycerin. This condition of limited activity and a narrow margin of cardiac reserve continued into 1931, when on February 18th he was seen at home in an attack of substernal pain so severe and prolonged that it was felt we were dealing with an occlusion instead of an attack of angina. This attack began about 5.00 p. m. and was first relieved

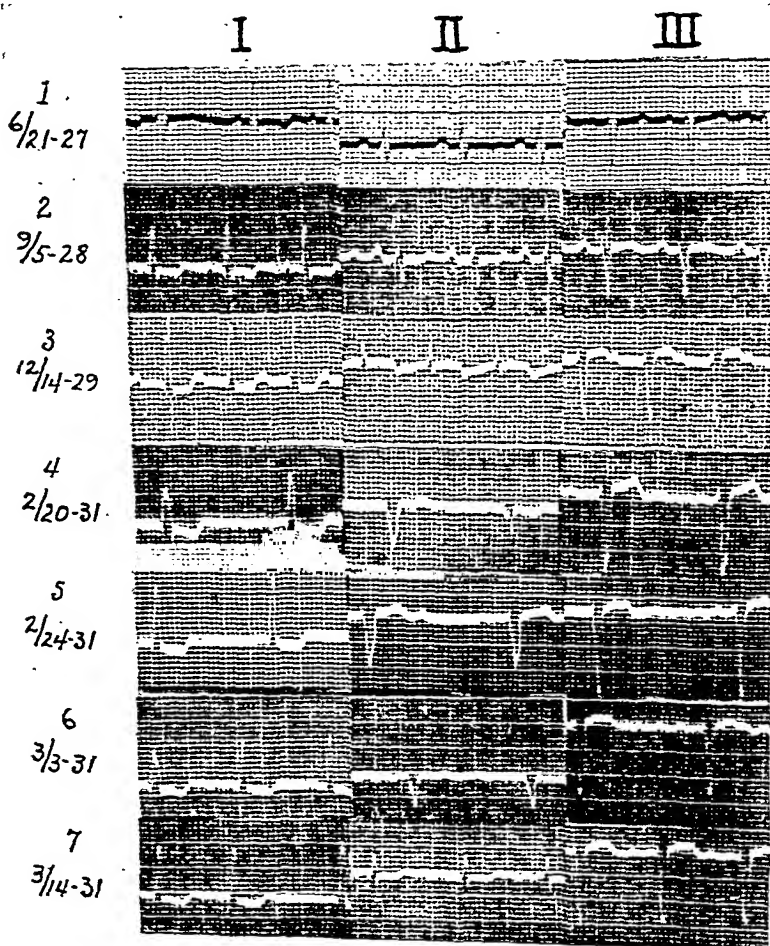


Fig. 95.—Case I. S. B. K.

by nitroglycerin, only to reappear about 9.15 and continue until after the administration of morphine. The patient was pale, sweating and immobile in the orthopneic position. There was no dyspnea, no cyanosis and no lung moisture. The blood pressure was 220/130 with a heart rate of 90. After he became relieved he stated that on February 9th, 14th, 15th and 16th he had noted moderate

thrombosis of the superior mesenteric vessels (primary arterial thrombosis) with infarction of the small intestine, early gangrene and fibrinopurulent peritonitis; old infarcts of spleen and kidneys, recent splenic infarct; arteriolonephrosclerosis, moderate; arteriosclerotic scars of the kidneys; chronic passive hyperemia and edema of the lungs; no infarcts found; chronic passive hyperemia of the liver, spleen and kidneys; bilateral chronic encysted fibrous and serofibrinous pleuritis; fibrous and caseous tuberculous scar of the right upper lobe of lung with bronchiectatic cavitation; extensive encephalomalacia (red and gray with necrosing cerebral arteriolosclerosis).

"The heart weighs 550 Gm., the apex is formed by the left ventricle which appears somewhat rounded. The pericardium is smooth and glistening. The subepicardial fat is fairly abundant. The left ventricle averages 14 mm. in thickness, the right 3 mm. The papillary muscles and columnae are thick and somewhat flattened. The endocardium is smooth and glistening but in the left ventricle appears grayish and opaque. In the region of the apex of the left ventricle adjacent to the septum the myocardium appears softened and mottled light purple-gray and red. The myocardium elsewhere is soft, purple-gray-brown except in the midportion of the outer wall of the left ventricle where it appears to be firmer, slightly yellow-gray. The coronary vessels are carefully dissected and reveal atheromatous plaques throughout the intima with narrowing, especially of the anterior descending branch of the left. There are no evidences of thrombotic occlusion of any vessel. The valvular apparatus reveals no changes. The mouths of the coronaries are freely patent. The aorta reveals moderate arteriosclerotic changes, especially marked at the bifurcation of the iliac vessels. Both auricular appendages contain firm adherent mottled, purple-gray and purple-red masses.

"The peritoneal cavity contains about 100 cc. of bloody, turbid fluid. The serosal surfaces, especially of the small intestines, are dull and hemorrhagic, covered with a loose, friable, cobwebby, gray-yellow membrane. The small intestine, especially the ileum, is markedly distended, deep purple in color.

"The vessels to the discolored bowel, namely, the superior mesenteric artery and its branches, are occluded by firm, adherent mottled, purple-gray and purple-red masses. The superior mesenteric vein is distended, firm."

The essential findings in the brain, after hardening in formalin, are: "The inferior convolutions of the island of Reil show marked softening involving both white and gray matter, on the left side, as do the superior and medial temporal, and inferior parietal convolutions. At the level of the junction of the superior marginal and angular gyri posterior to the level of the amygdaloid nucleus, there is also extensive softening extending similarly to the region of the endypma. Extensive softening involves the lateral occipital gyri and the inferior parietal lobe. On the right side at this level softening is similarly present in the inferior parietal lobe. Along the calcarine fissure, approximately 2 cm. from the posterior tip of the occipital pole, is a 3 x 2 x 1 cm. area of softened red-brown tissue. In the lobus diventer of the left cerebellar hemisphere is an area of yellow-gray and red softening."

Case II.—A. C. G., a salesman, aged sixty-three, was first seen March 29, 1927, because of cervical arthritis. His past history was meager and included

attack of substernal pain, necessitating another dose of morphine. When seen at 9.00 A. M. he was again comfortable with a blood pressure of 165/80 and a heart rate of 76 and a slow auricular fibrillation. He was removed to the hospital in an ambulance and there showed a temperature of 99.1 F., heart rate of 66 to 70 and a leukocytosis of 13,500. Electrocardiograms were made on February 20th and 24th (Fig. 95, 4, 5) which showed the development of auricular fibrillation, complete auriculoventricular block and also a more marked left preponderance. He left the hospital March 19th and remained in bed at home for three weeks, maintaining comfort with no significant heart symptoms manifested.

Electrocardiograms made on March 3rd and 14th (Fig. 95, 6, 7) disclosed persistence of the myocardial damage and lessening of the left ventricular preponderance.

During the summer he was able to look after his law practice and by the use of digitalis, nitroglycerin and aminophyllin maintained a very satisfactory, if limited, state of efficiency. He again went to France in August, 1931, where on September 5th he had a very grave decompensation, from which he emerged with a marked sensory aphasia which persisted until his death. The French physician, who courteously sent me data on this illness, did not state the blood pressure at this time but left no doubt as to there having occurred a severe acute pulmonary edema.

He returned to Chicago on October 18th. It was difficult to give him very satisfactory care because of the aphasia which was entirely sensory. Words were meaningless and one had to deal entirely objectively as does the veterinarian. From October 18th until December 23rd there was little change. On this latter date I saw the patient about 1.00 A. M. suffering pain apparently under the sternum, pale, vomiting frothy fluid, with a heart rate of 125 to 130 and respirations 32. Moderate basal moisture was revealed in the lungs. Morphine brought some relief and the patient was fairly quiet the balance of the night. Seen again at 9.00 A. M. the blood pressure was 210/130, heart rate 88, with auricular fibrillation and only his average amount of moisture was noted in the lung bases. At 5.00 P. M. his pressure was 200/130 and he had had a comfortable day. There had occurred two attacks of vomiting of colorless material. The heart varied between 96 and 100 with auricular fibrillation still present. During the night he coughed much bright blood and when seen at 9.00 A. M. on December 24th he was very restless and had a temperature of 101.2 F., heart rate of 84. The tones were quiet, the pressure was 160/90. It was felt that another coronary occlusion had occurred and morphine was used sufficiently to maintain comfort. His progress was steadily downhill and a hypostatic pneumonia was thought to have developed because of the temperature and moderate dulness and moisture in the lungs. Mental dulness and irrationality gradually increased. On January 6th he manifested great and continuous pain but it was impossible to determine anything of its location or nature because of the aphasia. Death occurred very quietly about 3.00 A. M. on January 7th. Autopsy was done at the undertaker's at 10.30 A. M. by Dr. A. A. Wolfson whose relevant findings follow:

"Pathological Diagnosis.—Generalized arteriosclerosis with marked coronary sclerosis and extensive myocardial fibrosis (small healed infarcts); hypertrophy and dilatation of the heart with mural thrombi of both auricular appendages;

Examination disclosed that he was 64 inches tall and weighed 180 pounds. His complexion was florid. The heart extended 10.5 cm. to the left and 4.5 cm. to the right on a 2-meter plate. The lungs were clear. The heart tones were vigorous and a systolic murmur was heard over the aortic arch. The blood pressure was 175/110. Urine examination was negative for albumin, sugar and casts. Wassermann was negative. A diagnosis of hypertensive heart disease was made. He was seen at reasonable intervals and his progress up to September, 1931, was uneventful except for an attack of lobar pneumonia for which he was hospitalized from December 23, 1930, until January 8, 1931. The accompanying graph shows the blood pressure range during these years (Fig. 97). The chemical findings in his blood and phenolphthalein output were only moderately at variance from normal. However, there was a tendency to the development of moderate dyspnea on exertion and in March, 1931, extrasystoles were noted at times. The 2-meter heart plates showed a gradual increase in the cardiac size (CTR on graph).

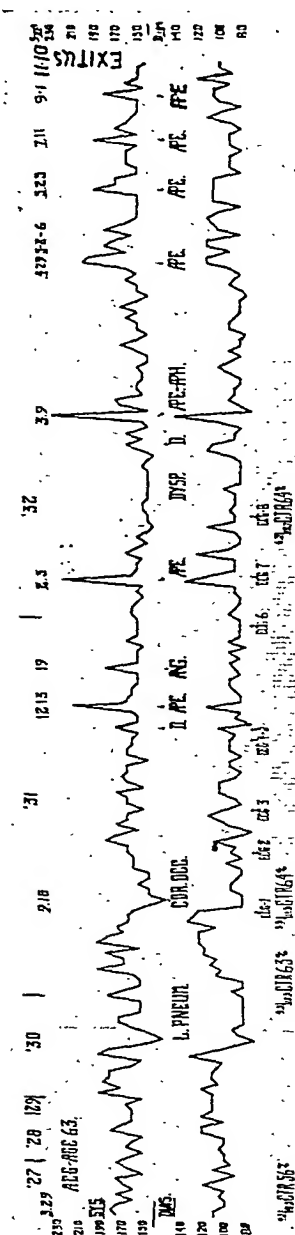
On September 11, 1931, he reported difficulty in sleeping on account of dyspnea which at times awakened him. His blood pressure on this date was 155/115, the heart tones showed no change and lung base moisture was very slight.

On September 17th he went to the hospital for a 2-meter heart plate, electrocardiogram, blood count and phenolphthalein estimation. His temperature was normal. His leukocyte count was 10,500 and his dye elimination was 5 per cent in the first hour and 10 per cent in the second hour. The 2-meter plate revealed "cardiac hypertrophy and infiltration of the right and left base secondary to cardiac decompensation."

The first electrocardiogram was made September 17, 1931, and showed a left axis shift and myocardial damage.

That night at home he was very uncomfortable because of dyspnea and cough with moderate amounts of bloody sputum. Seen on the 18th at 1.00 p. m. he showed a temperature of 101.2 F. with a pulse of 90 and a blood pressure of 145/80. He was hospitalized and it was found that his leukocyte count was 27,000 with neutrophils 93 per cent. On the 21st the leukocytes were 11,850. His temperature varied between 98.3 and 102 F. up to the 23rd when it went to normal and remained there, the patient going home on September 26th. It was felt at the time that a hypostatic pneumonia rather than a bronchopneumonia was present. In the light of subsequent events and findings it is noteworthy that pain was entirely absent. On the 25th, the day prior to discharge, another phenolphthalein estimation was made and, having been thoroughly digitalized by this time, the dye return was 30 per cent in the first hour and 20 per cent in the second hour. The blood urea was 16.8 mg. and the creatinine 2.01 mg. His heart rate on discharge was 52 and the blood pressure was 155/85. Having had no digitalis after September 23rd it was interesting to note regularly coupled beats on October 8th, and still find moderate dyspnea and occasional cough with blood-tinged sputum. The rate was 84 and digitalis was then given twice daily (1.5 grain of the powdered leaf).

Observed on October 12th and 19th he manifested improvement and yet the coupled beats were present. Digitalis was discontinued on the 23rd. Electrocardiogram of October 23, 1931 (Fig. 98, 2), showed regularly recurring right



attacks called pleurisy ten or fifteen years before, several attacks of tonsillitis and removal of the tonsils two months before this date.

showed Cheyne-Stokes respiration. Lung moisture was only moderate—fine moist basal râles. The liver was never found below the costal border and skin edema was only slight. Despite the use of morphine and one of the theobromine group he became more uncomfortable. On the 30th he was placed in the oxygen tent, though showing no cyanosis, and the benefit was almost immediate and continuous. He was very hard to control and would insist on getting out of the tent; only to become so dyspneic that it was not difficult to persuade him to reenter it. The electrocardiogram November 2nd (Fig. 98, 3) shows a condition similar to that of October 23rd. The heart rate was 84, and since he had had no digitalis and the heart clinically was failing it was decided to resume this drug. Within two days it was apparent that he was definitely improving and the following from the progress notes makes clear the deductions concerning the events developing on and after September 17th. "Reviewing the factors of a fairly sudden heart disability beginning September 18th, with no marked cardiac symptoms previously, with marked cardiac failure, lowering of the blood pressure, leukocytosis and the evidence of the electrocardiograms, I believe one may postulate a silent coronary occlusion of a branch of the coronary (anterior descending branch of the left coronary)."

From the time of the resumption of digitalis his improvement was steady and he was able to be out of the tent for greater periods without discomfort. The electrocardiogram (Fig. 98, 4) made on November 17th suggested that we were dealing with an occlusion and that repair was taking place.

The patient was discharged on November 19th, being able to walk 200 feet without any dyspnea. However, on December 2nd he reported that he had noted some dyspnea and once moderate substernal pain (angina). His heart rate varied between 76 and 84 and extrasystoles were noted, and basal moisture was again present. By December 6th his cardiac reserve had failed to the degree that orthopnea was present and Cheyne-Stokes respiration was again observed. He was readmitted to the hospital December 9th with a diagnosis of cardiac decompensation and placed in the oxygen tent. His phenolphthalein output was 40 per cent in two hours; the blood urea was 7 mg. and creatinine was 1.4 mg. The electrocardiogram taken on December 9th (Fig. 98, 5) showed recurrence of ectopic impulse from the right ventricle and increasing myocardial damage. Again he improved and on December 12th the record notes "a good day. Still basal moisture. Blood pressure 155/80." However, at 4.00 A. M. the next day he was observed in an attack of acute pulmonary edema with orthopnea, heart rate of 100, a blood pressure of 208/110 and the lungs were filled with coarse, moist râles. The sputum was bloody. Digitalis and morphine controlled the situation and at 9.00 A. M. his pressure was down to 160/80 and the heart rate was 64. He was pale but no cyanosis was observed. At 6.00 P. M. he was still comfortable and had had a satisfactory day. His breath had a uremic odor and periods of Cheyne-Stokes breathing and low urine output occurred. By the 15th his urine output had increased to 2700 cc., the ectopic beats had almost disappeared and improvement was very decided. Between December 18th and 25th he frequently complained of substernal tightness which never progressed to the degree of actual pain except on December 23rd when he had an attack of real angina lasting fifteen or twenty minutes. The use of aminophyllin served well, since there has been no further complaints of these

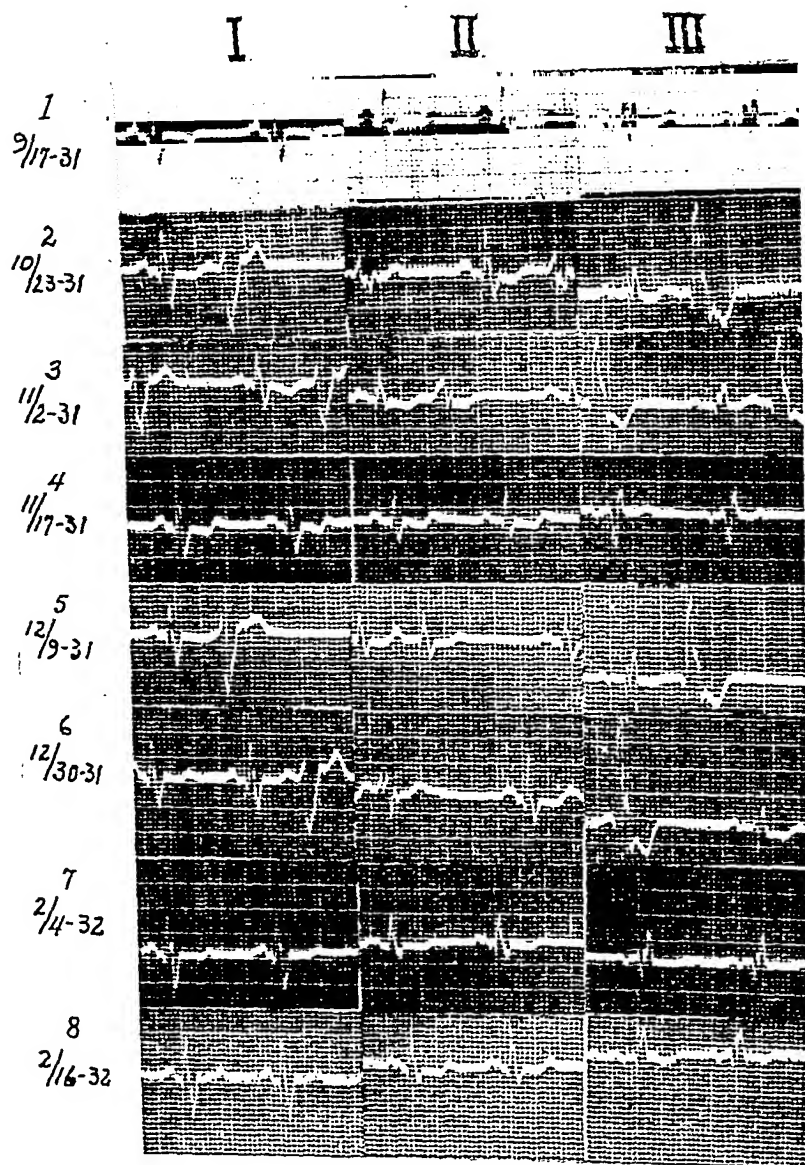


Fig. 98.—Case II.

ventricular ectopic impulses resulting in a pulsus bigeminus and myocardial damage. His discomfort increasing, he was readmitted to the hospital on October 26th and not only was he dyspneic but orthopneic and not infrequently

July, but on July 11th he was seized with an attack of acute pulmonary edema which came on without warning at about 7.30 P. M. during which his pressure rose to 190/90. The last attack occurred on September 1st, with the pressure being recorded at 180/110. Throughout September and October there was manifested increasing mental confusion and periods of marked mental irritability, with an increase of edema of the legs, probably due to myocardial failure and to the fact that he would sit in his chair sometimes for days, and at least for twenty out of the twenty-four hours at other times. The liver and lungs never showed further engorgement and the oxygen tent was unnecessary. Morphine was used at varying intervals, sometimes three times in twenty-four hours, and again as infrequently as once in sixteen hours, its use probably necessitated by habit rather than because of any observable physical discomfort. However, on November 2nd, a condition of dementia developed in which he became violent and opiates and sedatives were demanded in huge and frequent doses to control him. He was removed to the hospital on November 6th and was kept in a somnolent and controllable condition until his death which occurred on the 10th from a terminal bronchopneumonia. The sudden onset of this dementia suggested new cerebral developments in the silent area of the brain such as embolism or new occlusion, but the cardiac findings did not indicate any change in that organ. During his last two months of life there had been manifested only a slow auricular fibrillation with a heart rate varying between 60 and 72. No digitalis was given during this period.

The autopsy was done by Dr. John L. Sullivan, from whose report the following essential data are cited:

1. Marked generalized arteriosclerosis.
2. Marked coronary sclerosis. Old infarction of the myocardium.
3. Arteriosclerosis of the arteries of the base of the brain.
4. Multiple areas of encephalomalacia; arteriosclerotic atrophy of the cortical portions of the brain.
5. Nephrosclerosis, arteriolar variety.
6. Hypertrophy and dilatation of the heart.
7. Pulmonary emboli; infarcts in the right lung; pulmonary thrombi (small vein).
8. Bronchopneumonia.

"The heart is greatly enlarged, weighing 700 Gm. There are several, up to 1 cm. in diameter, hemorrhagic areas just beneath the epicardium. There are also present several irregular gray-white areas over the left ventricle, and in the apex of the left ventricle there is an irregular gray-white area measuring about 1 cm. . . . In the apex of the left ventricle there is a pink-gray irregular intramural thrombus firmly attached to the myocardium. . . . The mouths of the coronaries are patent. The coronary vessels are sclerosed with narrowing of the lumina, the right circumflex branch showing marked sclerosis. In the right auricular appendage there is an irregular, firm, pink-gray thrombus, firmly attached to the auricular endocardium. The left ventricular wall measures about 12 mm., the right, about 3 mm. . . . The aorta is inelastic and dilated in the first portion, and shows only a few yellow plaques of intimal thickening. Beginning at the arch and extending down to the bifurcation of the aorta there are many yellow plaques of intimal thickening with large areas of atheromatous ulcera-

attacks. The use of the oxygen tent was stopped on December 26th and he was able to leave the hospital on January 1, 1932, with a satisfactory ability to move about, a blood pressure of 150/85, heart rate 68, slight moisture in the lung bases and no engorgement of the liver and no shin edema. He progressed very comfortably for a month and then developed another attack of acute pulmonary edema on February 3, 1932. On this date it was decided to have him go to the hospital for a 2-meter plate and an electrocardiogram. He complained of increased dyspnea at about 10.00 A. M. but was driven to the hospital about 1.30 P. M. and while in the car became acutely dyspneic, ashy-gray, perspired profusely and gasped for breath. On his admission he was at once placed in the oxygen tent and morphine and digitalis were administered. His blood pressure which had been 145/80 was found to be 230/130, his heart rate was 140 and the chest was full of coarse moist râles. His exitus seemed imminent, but oxygen, morphine and digitalis manifested their value and by 6.00 P. M. he was very comfortable with a heart rate of 84 and a blood pressure of 145/80 and absence of cyanosis. His improvement continued through February 4th to 7th but, as was stated before, he was very difficult to control and would get out of bed. On the 9th the progress notes state that he had had a poor night with more dyspnea and Cheyne-Stokes respiration and the blood pressure showed a rise of the diastolic pressure (160/120) with weak heart tones and a rate of 90. Later in the day moderate cardiac asthma with bloody sputum was noted but these symptoms abated and his condition gradually improved to the degree that he was able to leave the hospital on February 17th. The electrocardiograms made on December 30 (Fig. 98, 6), February 4 and 16, 1932 (Fig. 98, 7, 8), revealed only progress of the cardiac damage.

It became very apparent that the oxygen tent was indispensable and he bought one for use at home. Morphine had to be used regularly and digitalis from time to time. Despite scanty physical findings there were frequent periods of dyspnea and Cheyne-Stokes respiration induced by the most moderate activity. It will be noted on the graph (Fig. 97) that his systolic and diastolic pressures were unusually low for him after the last attack of acute pulmonary edema, probably due to his low cardiac reserve. He spent at least twelve out of every twenty-four hours in his oxygen tent. On March 3rd and 4th his pressure rose to 160, accompanied by increased dyspnea, coarse moist râles in the chest and bloody sputum. Digitalis to the amount of 12 grains of the powdered leaf was given in twenty-four hours and the threatening attack disappeared. However, on March 9th, he was again seen in an attack of acute pulmonary edema at 8.00 A. M. with his pressure 230/140 and all the characteristic signs present, *although he had been in the oxygen tent all night*. Morphine and digitalis again apparently served well, for by 6.00 P. M. his pressure was down to 140/70 and he was very comfortable. The next day he was mentally confused and a sensory aphasia became manifested (APE-APH) which has persisted, and which, as in the first case reported, has made communication with him very difficult. No special developments arose until April 29th when another attack of acute pulmonary edema occurred, with the pressure 200/110, gradually dropping to and remaining at 150 for about ten days, only to be followed by yet another attack on May 25th which also cleared promptly.

The pressures showed a period of low levels throughout June and early

are related to attacks of cardiac asthma (D) or to the dramatic picture of acute pulmonary edema (APE).

4. In Case I, angina (ANG) recurred very frequently after its appearance in May, 1930, while in Case II this was present only for a week in 1931.

5. The development of a sensory aphasia (APH) in each case immediately following an attack of acute pulmonary edema and the high rise in blood pressure is a curious coincidence. One might assume the cause to be embolic; yet study of the brains revealed only sclerotic changes. It might be well to emphasize that occlusion of a vessel, cerebral or coronary, may occur suddenly from sclerosis and not be due to thrombosis. This was true of the coronary occlusion in Case I where the left anterior descending branch was occluded, but showed no evidence of a thrombus. In this case the terminal condition, beginning on December 23rd, is a confusing picture, the symptoms of which it is difficult to correlate. In the first place the initial symptoms being those of apparent substernal pain, with vomiting, tachycardia and increased respiratory rate and lung moisture seem unrelated to a definite picture of mesenteric thrombosis. The coughing of bright blood later, with development of temperature and restlessness fitted into the belief that a coronary occlusion had occurred. On the other hand we know from the autopsy that there were auricular appendage thrombi and mesenteric thrombosis, with infarction of the intestines, early gangrene and fibrinopurulent peritonitis. Yet if this terminal occurrence began on December 23rd, one would expect death to have occurred in a much shorter time than the two weeks which did intervene, unless there was a small infarction at first, with repeated insults in the following two weeks. The abdomen never became markedly tympanitic or rigid, nor was there any visible blood in the stools as one might expect. It is possible that if the patient had been able to talk his subjective symptoms would have greatly clarified the picture.

In Case I, although there had been known hypertension for fifteen years, the onset of cardiac failure occurred in 1927, yet required five years to develop completely, during which interval the patient lived a modified, but useful life.

tion and calcification. In the first portion of the descending aorta there are several areas of ulceration with clotted blood between the intima and media. There is beginning necrosis of the intima and media in these areas."

In the brain "there is marked sclerosis of all the cerebral arteries with narrowing of the lumina, but no definite occlusion is found. In the region of the posterior portion of the parietal lobes close to the longitudinal fissure extending bilaterally over an area of 6 cm. in diameter there is a depression involving the precentral and central gyri, and corresponding fissures." After formalin hardening, "the brain on section reveals in the region of the superior gyrus of the left temporal lobe an area of softening primarily confined to a region close to the isle of Reil. It also extends toward the capsula extrema but does not involve the capsule itself or the lenticular nucleus. Posteriorly it extends up to the region of the posterior horn of the lateral ventricle involving also the white substance in this region, but not actually reaching the wall of the posterior horn of the left lateral ventricle. The area described before the brain was cut reveals only an atrophy of the gyri, but no evidence of necrosis or hemorrhage."

Heart (microscopical examination): "There is a marked increase in connective tissue throughout all sections. . . . Sections through the mural thrombus and infarction of the left ventricular apex show the thrombus to be composed of fibrous and connective tissue in which are enmeshed red cells, polymorphonuclear leukocytes, lymphocytes, mononuclear and endothelial cells with a small amount of brown, granular pigment. . . . The branches of the coronary arteries in the section showed a markedly thickened wall."

Lungs (microscopical examination): "All the blood vessels are filled with red cells and in a few of the smaller veins thrombi are seen. There is a moderate increase in perivascular connective tissue. The right lung weighs 800 Gm. On section the surface of the lung is moist, dark red in color, and in the upper lobe there is a well-demarcated area which is pinkish-gray, firm to touch, and granular. This surface is more dry than the rest of the lung surface. In the lower lobe of the right lung several of the smaller vessels are occluded by emboli, and in these areas the lung surface is dark reddish black with obscure architecture. The left lung weighs 725 Gm."

COMMENT

These graphs emphasize the value of keeping records of the progress of a case and of visually connecting the various events developing during that progress. Several features engage the attention in these two graphs:

1. A reasonably consistent parallélism of the systolic and diastolic pressures.
2. The diastolic pressures average much lower than those commonly observed in cases with marked renal damage.
3. Sudden and exaggerated rises of the systolic pressure, usually with an accompanying rise in the diastolic pressure,

are related to attacks of cardiac asthma (D) or to the dramatic picture of acute pulmonary edema (APE).

4. In Case I, angina (ANG) recurred very frequently after its appearance in May, 1930, while in Case II this was present only for a week in 1931.

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In Case I, although there had been known hypertension for fifteen years, the onset of cardiac failure occurred in 1927, yet required five years to develop completely, during which interval the patient lived a modified, but useful life.

However, in Case II, with no evidence of a protracted hypertensive condition, he lived as usual for four and a half years after his vessel changes were discovered, only to rapidly become and remain a complete invalid after a coronary occlusion occurring in September, 1931. It is very clear that a coronary occlusion is not infrequently the beginning of a persistent and fatal cardiac breakdown, due to the great damage the myocardium must suffer because of the infarction. In this case is evidenced the great value of oxygen therapy, but it is interesting to note that three of his attacks of acute pulmonary edema (December 13, 1931, March 9 and April 29, 1932) came on while in the tent or shortly after coming out of it.

In these histories are illustrated the three stages of heart failure described by Vaquez:¹ (1) Dyspnea of effort; (2) cardiac asthma (D), with urgent dyspnea and increased pulmonary secretion, blood tinged, and (3) acute pulmonary edema (APE), sudden in onset, dramatic and terrifying in the intensity of its symptoms which seem to be a heightening of those of cardiac asthma. It seems definite that all of the various terms applied to this sudden cardiac failure are only efforts to distinguish varying degrees of the same process—cardiac failure due to coronary sclerosis and myocardial degeneration.

Just what the mechanism of these varying degrees of dyspnea is seems to be a moot question. Whether it is due to disproportion in the working power of the two ventricles in which the left ventricle is unable to expel in a unit of time the same quantity of blood as the right heart, as was suggested by Welch² in 1878; or whether it may be due to an abrupt and marked rise in the blood pressure with the heart already overburdened by a hypertension and unable to cope with this added load as Fishberg³ suggests, seems to me to be undeterminable clinically. It would seem reasonable that with the right heart placing an overload upon the left ventricle sufficient to cause the pulmonary symptoms, one should more often observe engorgement of the liver, fluid in the peritoneal cavity and even dependent edema. In neither of the two patients reported has the liver been found below the costal border, nor has there been evidence of ascites,

and only since his attack of acute pulmonary edema in July has Case II shown dependent edema in the legs, largely due to enforced inactivity. With this marked leg edema there is no passive congestion of the lungs or enlargement of the liver.

Regarding the repeated acute, temporary rises of the systolic pressure during the attacks, again conjecture and hypothesis are all one may offer. Pratt,⁴ discussing cardiac asthma, makes four groups: (1) Pure cardiac asthma, the severe cases of which manifest agonizing attacks of suffocation. (2) Mixed anginous form—cardiac asthma with angina pectoris. (3) Mixed edematous form—cardiac asthma with pulmonary edema. (4) The combined form—cardiac asthma with angina and pulmonary edema. He cites several cases of severe cardiac asthma where the pressure rose during the attack and subsided with relief, and quotes Osler to the effect that the pressure may rise to 330 mm. He cites also Amblard who reported 4 cases of acute edema of the lungs in which the pressure rose to 240, 250, 270 and 280, respectively. Pratt cites some of the theories as to the cause of this condition, but like others is unable to arrive at any satisfactory explanation.

Wiggers⁵ says that whenever systolic discharge of the right heart exceeds that of the left, as may conceivably happen either when the systolic venous flow increases or systolic arterial resistance is greatly raised, intense pulmonary congestion must inevitably occur unless compensatory mechanisms are set in operation.

In view of the pulmonary infarctions found in these autopsies one might speculate with the thought that in each attack of cardiac asthma and pulmonary edema there might have occurred enough infarction to account for the bloody sputum, and vasomotor irritability to cause the rise in blood pressure. Certainly the usual concept that in cardiac failure there is a vasomotor impairment with a falling blood pressure is disproved in these graphs, and the coincidence of a left ventricular failure with a marked rise in systolic pressure suggests that the vis a tergo is only one of the factors involved. The observation of the rise in blood pressure in Case I during an attack of Vincent's

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angina (V-ANG) when there was no evidence of cardiac failure suggests that pain and pain-effort as is noted in cardiac asthma may stimulate the sympathetic nerve and induce peripheral spasm, thus raising the blood pressure.

SUMMARY

1. Two patients observed over a period of five years, with blood pressure readings numbering over 200, showing repeated attacks of acute pulmonary edema.

2. Accompanying each of these attacks there was noted a rapid and high increase of the blood pressures at the time the heart showed the greatest failure, with rapid decline as compensation was restored.

3. Following one of the attacks of acute pulmonary edema each patient emerged with a sensory aphasia which persisted for many weeks until death.

4. Each of these patients suffered a coronary occlusion, one characteristic with pain; the other, a silent attack. Autopsy disclosed that neither of these was due to thrombosis but to arteriosclerotic narrowing.

5. Autopsy in each case revealed widespread arteriosclerotic changes, involving also the brain vessels.

6. These cases show the value of making notes at each interview and graphically recording the related data.

7. It is hoped others will be stimulated to collect information of this character in the course of their daily work and, perhaps, lead to a more thorough understanding of the events recorded.

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4. Pratt: *Jour. Amer. Med. Assoc.*, 1926, 87, 813.
5. Wiggers: *Modern Aspects of the Circulation in Health and Disease*, 1923.

curve. Cultures made from proctoscopic material were negative for members of the typhoid and dysentery groups of organisms. A total of ten stools were cultured in an attempt to isolate Flexner or other types of dysentery bacilli but all were negative also. The patient's serum, however, agglutinated a strain of known Flexner organisms in dilution to 1 to 320. From both proctoscopic and stool cultures, heavy growths of Bargaen's diplococcus were obtained.

On roentgenological examination, a marked narrowing of the lumen of the entire colon with lack of haustrations was demonstrated.

Treatment with Bargaen's antiserum (concentrated) was begun immediately after the diagnosis had been established. In addition to the serum, a liver and iron preparation was given four times daily in 15-Gm. doses. During the first nineteen days in the hospital her temperature rose daily to 99.8 F. After that it remained normal during the rest of her stay.

The patient made a gradual recovery, gained 23 pounds in weight, and now feels well and seems to be in excellent health. The stools number from three to four a day and vary in consistency from mushy to soft formed. There have been intervals of a week or more during which blood in the stools has been absent, but when blood does occur it is in the form of streaks on the more formed stool. Proctoscopic examination at the present time can be done easily with the adult-sized instrument. The mucosa is of normal color, finely granular with a slight amount of pitting; low in the ampulla are still a few pin-point ulcerations which bleed easily on wiping over them. The blood picture has returned to normal in all respects. Roentgenologically an increase in the caliber of the colon down to the lower sigmoid is noted.

Case II.—Miss L. D., a saleslady, aged twenty-eight, entered the hospital on September 22, 1932. Other than for a pelvic infection for which she was operated in 1927, the patient had been in good health until the onset of her illness which brought her to the hospital. Three months prior to her admission she began to notice lower abdominal cramping lasting a few minutes and coming on at various intervals during a day. About ten days later her stools, which up to this time had been normal, became watery, very dark colored, and were from four to five a day in number. On one occasion during the following week she vomited a large amount of dark-colored material. The combination of symptoms made her very weak and she had to remain in bed for three weeks. In the following eight weeks she vomited on six different occasions and always there was a variable amount of bright red blood present in the vomitus. The last of these had occurred two days before her admission. A week after the onset of the diarrhea the number of stools increased to about ten a day along with a gradually increasing amount of mucus and bright blood. During this entire time she had lost twenty pounds in weight, weakness increased, and her skin became increasingly pale. With the increase in the number of stools there appeared a daily fever ranging from 101 to 102 F. On entrance the patient appeared extremely ill. There was marked pallor. A low grade salpingo-oophoritis was noted on pelvic examination.

The laboratory findings were as follows: The Wassermann and Kahn tests were negative. The leukocyte count was 7600 with a lymphocytosis of 49 per cent. The erythrocytes numbered 3,240,000, with considerable polychromasia

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ULCERATIVE COLITIS

THE two cases to be presented have been chosen to illustrate certain aspects of non-specific ulcerative colitis. They differ in their clinical manifestations, in their course, and in the type of therapy employed.

Case I.—The first case, Miss D. L., a twenty-year-old school girl, was admitted to this hospital on July 6, 1932. Her history was that of a rather sudden onset of an attack of diarrhea seven years previously following some dietary indiscretion. The stools were watery and numbered from five to six daily. The frequency of bowel movements persisted for about a week, after which time they increased in number to ten or more a day. Blood was now being noted in the rectal discharges in gradually increasing amounts, which in the course of another week reached an alarming degree. She then saw her physician, who advised her to enter the hospital and diagnosed her condition as ulcerative colitis. She remained in the hospital for five weeks, during which time her treatment apparently consisted chiefly of rest, dietary management, and silver nitrate enemas. At the end of this time she became symptom-free and remained so for nearly four years. An intermittent diarrhea then appeared and persisted during the three years prior to her admission to this hospital. The periods of remission did not exceed a week in duration. During this time she received various types of medication, all of which were ineffective. There was a gradual increase in weakness and progressive loss of weight. At the time of her admission here she was having eight to ten watery mucopurulent and bloody stools a day. The general physical examination was negative except for a marked pallor and an appearance of being very ill. Proctoscopical examination was attempted but the bowel lumen was so narrowed that even with the smallest instrument, not more than 10 cm. of the bowel could be examined. The mucosa was extremely friable and granular. Numerous shallow ulcerations could be seen ranging from 2 to 3 mm. in diameter and exuding blood and pus.

The laboratory findings were as follows: The Wassermann and Kahn tests were negative. The leukocytes numbered 7600 per cubic millimeter, with a normal differential count. The erythrocytes were polychromatic and anisocytotic with a total count of 3,890,000 per cubic millimeter and a hemoglobin of 36 per cent (Sahli). The urine examination was normal. Gastric analysis after histamine injection showed 30 clinical units of free HCl at the height of the

numerous cases are seen in which the entire colon is affected. Barger describes, however, instances in which localized portions of the colon are involved and are demonstrable only by roentgenological study. The disease in general presents rather constant clinical manifestations and anatomical changes. The course may be a rapidly fatal one or it may be more or less chronic with periods of remission and exacerbation.

The first case is an illustration of the more chronic type. From the history one is immediately led to suspect an inflammatory process in the bowel, dating back over a number of years. The first symptoms were not of an alarming nature. This is frequently the case. At first there is a rather mild persistent diarrhea which gradually increases. Along with the increase in diarrhea, the rectal discharges become mixed with blood, pus, and mucus to a varying degree. In this instance, the patient stated that in the beginning she thought she was having just the ordinary type of diarrhea following some dietary indiscretion and she was not worried by it. However, after about a week when she began to notice blood in the stool, she became alarmed. Very frequently it is not until this occurs and the process is well under way that the patient seeks the aid of a physician. As the condition advances in severity there then begins a more or less rapid loss of weight and an increasing weakness. The appetite becomes poor and the patient presents in general the picture of a severe wasting disease. Due to the continuous loss of increasing amounts of blood in the stool, a secondary type of anemia develops which may reach an alarming degree.

The more acute form of the disease process, as well as the degree of prostration such a patient may exhibit, is illustrated by the second case. Here again the symptoms in the beginning gave little concern. However, within a period of little more than two months she was so dangerously ill that little hope was held out for her recovery, and blood transfusions were given as a more or less hopeless gesture. Ringer's solution was given subcutaneously in large amounts and within four days a marked improvement was noted. From this time on recovery was grad-

and achromia; the hemoglobin was 25 per cent (Sahli). No abnormal cells were seen. Blood cultures taken on two different occasions were negative. The urine examination was negative. Blood agglutination tests for *Bacillus melitensis*, *B. abortus*, typhoid groups, Shiga and Flexner bacilli were negative. The bleeding time was four and one-half minutes and the clotting time, four minutes. Smears of several stools were studied for tubercle bacilli but none could be demonstrated. Guinea-pigs inoculated with stool from this patient were killed after six weeks but no evidence of a tuberculous process was found in these animals.

Because of the history suggesting gastric hemorrhage, the patient was immediately placed on "Sippy management." There was no vomiting, neither was the abdominal distress affected. Thus after a few days of observation on this régime, the presence of a gastric or duodenal lesion seemed doubtful and it was thought safe to proceed with a more detailed examination. Roentgenological studies of the stomach were made but no gross lesion could be demonstrated.

On proctoscopical examination the bowel mucosa appeared rather coarsely granular and was extremely easily injured. Numerous pin-head-sized ulcerations were present. Stool and proctoscopical material were cultured from which good growths of *Bargen's diplococcus* were isolated. As in the preceding case, these organisms gave the morphological, cultural, and fermentation characteristics as described by *Bargen*.

In the roentgenograms of the colon lack of haustral markings over the entire colon including the cecum are noted, a finding which is compatible with that of ulcerative colitis. The chest was normal roentgenologically. It was, therefore, assumed that the condition here was not that of a tuberculous enteritis. Furthermore, as stated above, the guinea-pig inoculations and examinations of the stools for tubercle bacilli were negative.

For the first fourteen days in the hospital, the afternoon temperature rose to between 100 and 101 F., but suddenly it began to range between 103 to 105 F. The patient became dangerously ill. A blood culture done at this time was negative. On the nineteenth and again on the twenty-first days transfusions of 500 cc. of citrated blood were given but the response to these was temporary. Daily hypodermoclysis of 1500 cc. of Ringer's solution for the next four days was followed by a considerable drop in the patient's temperature, and she began to show some signs of improvement. Abdominal cramping was severe and could be controlled only with morphine. Gradually these subsided and at the time of her discharge on December 4th she was having one formed stool a day without gross blood. The red blood count has increased to 4,100,000 with a hemoglobin of 5 per cent (Sahli). This patient received none of the so-called "specific" types of therapy. Proctoscopically there is noted at the present time a slightly injected mucosa which still has a tendency to be easily injured, a slight amount of pitting, and a very little of the granular appearance. No gross ulcerations are to be seen.

DISCUSSION

It is, of course, well known that ulcerative colitis is a serious depleting infection. Primarily it involves the lower colon but

appear normal but localized areas of disease can be demonstrated higher up in the colon roentgenologically.

Figure 99 shows the appearance of the barium-filled colon of Case I at the time she was first admitted to this hospital. It will be noted that the normal haustrations are entirely lacking and the bowel appears rigid. There is marked narrowing of the lumen, especially in the lower sigmoid. Figure 100 illustrates the present appearance of the same case. It is noteworthy



Fig. 99.—Roentgenographical appearance of colon of Case I at the time of admission.

that even though this patient has been practically free from symptoms for the past six months, there is no striking change in the roentgenographical appearance of the colon. The bowel lumen has increased some in size but the rather marked constriction in the lower sigmoid is still present. Figure 101 represents the roentgenogram of the barium-filled colon of Case II. Although there is a lack of haustrations over the entire colon there is not the marked degree of narrowing seen in the previous case. The outline of the colon is rather furred and ragged. The

ual, but progressive. Many of the patients of this type make just such a spontaneous recovery, but there are those who do not rally and die in spite of everything that is done for them. In contrast to the more chronic type of the disease the temperature reaction in these cases is apt to be marked. This patient, it will be remembered, had a daily fever ranging from 101 to 105 F.

The history of hematemesis and tarry stools in this case was at first misleading. However, she manifested none of these symptoms while in the hospital. The apparent gastric hemorrhage described in her history has not been satisfactorily explained. We have found no instance in the literature in which such a phenomenon has occurred in connection with ulcerative colitis. It is probable that there were minute gastric erosions or ulcerations, the presence of which could not be demonstrated radiologically.

Proctoscopically the two cases were very different. In the first patient there was a marked narrowing of the bowel lumen which was not so evident in the second. In both, the mucosa was friable, but in the first it was much more coarsely granular and the ulcerations were more advanced. The difference may be due to the fact that in the first patient the process had gone on for a long period of time. However, it is difficult to tell from proctoscopical examination during the acute stage whether the condition represents a sudden acute attack or an exacerbation of a chronic process. During a quiescent period the appearance proctoscopically is more uniform. The mucosa rarely becomes entirely normal; a finely granular or scarred appearance usually remains. Our two patients no doubt are now in a period of remission and the two proctoscopical pictures at the present time are much alike. The mucosa of both bowels is quite normal in color but it is still very finely granular with some pitting and some friability persists. Low in the rectum of the first case are a few minute bleeding points.

Roentgenological examination of the colon is a great aid in the diagnosis of ulcerative colitis. This is particularly true in those cases in which proctoscopically the rectum and sigmoid

(3) shortening of the colon. Where the ulcerations are quite deep, the outlines of the colon are furry and appear moth-eaten. Demonstration of the lack of haustral markings alone must not be taken too dogmatically as meaning the presence of ulcerative colitis. We have noted, on a number of occasions, that the roentgenological report has suggested the presence of ulcerative colitis involving the rectum and sigmoid, on the basis of the lack of haustral markings in cases in which no lesions could be demonstrated proctoscopically, and in which there was no other clinical evidence of such a process.

The etiology of ulcerative colitis has not been conclusively established. However, the disease picture is quite well recognized and the diagnosis is usually relatively simple. The origin seems to be an infectious one but the identity of the causative organism is still much debated. Various types of bacteria isolated in conjunction with the disease have been reported as contributing to its etiology. The dysentery group of organisms is said by a number of observers to play a considerable rôle in the production of the disease. This view is particularly upheld by the British investigators as well as to some extent by those on the continent. The fact that positive stool cultures and serum agglutination reactions are so rarely seen casts considerable doubt on the importance of this class of organisms in the etiology of the disease. It is interesting to note, however, that in Case I the blood serum possessed an agglutinin titer for Flexner organisms of 1 to 320. At no time could *Bacillus dysenteriae* be grown out in proctoscopic or stool cultures. The agglutination reaction of this patient's serum has been tested again at the present time and a positive reaction for Flexner bacilli again found. It is complete in a dilution of 1 to 160 and only partial in 1 to 320. It is a well-known fact that bacillary dysentery may become chronic and that it may then be very difficult to isolate the organisms from the stool. The morbid anatomy of chronic bacillary dysentery is identical with that of so-called "nonspecific ulcerative colitis." Consequently it must be admitted that some cases of ulcerative colitis may be in reality instances of chronic bacillary dysentery even though the organ-



100.—Roentgenogram of the colon of the same patient six months later.



Fig. 101.—Case II at the time of admission.

Most outstanding roentgenological signs of ulcerative colitis are
 (1) the lack of haustrations, (2) narrowing of the bowel lumen,

invariably develop a marked increase in their bowel disturbance. Even proctoscopically the bowel mucosa appears much more hyperemic. This local reaction lasts for several days and then subsides. There is no difference in this respect between those patients who respond satisfactorily to this type of therapy and those who do not.

The treatment used in the second case was extremely varied and was purely symptomatic. She was given two blood transfusions which were followed by hypodermoclysis of Ringer's solution. In addition the diet was for a time very low in residue and gradually increased as the patient was able to tolerate more food. To control the severe abdominal cramps she was given morphine, and as these subsided other sedatives were used. Kaolin was given for a period but seemed ineffective. Atropine, light therapy, and heat to the abdomen were also included. Had we introduced serum in the treatment of this case we probably would have been inclined to give it all the credit. At the present time this patient is just as well subjectively and objectively as the patient who received the serum.

Our experience with Barger's antiserum has not been entirely satisfactory. A number of patients have shown no improvement whatever. However, there have been several instances in which it has seemed likely that improvement of the patient could be attributed rather definitely to its effect. Until a definite etiology can be established we must continue to use the empirical forms of treatment.

isms are not present in the stools and the blood serum does not contain the specific agglutinins in high titer.

Since Bargaen's reports on the isolation of a diplostreptococcus directly from the lesions in ulcerative colitis and his apparent success in reproducing the disease in experimental animals, a great deal of interest has arisen in this possibility. A study of the literature, however, indicates that there is as yet no unanimity of opinion with regard to the importance of the diplostreptococcus. Cultures made from materials obtained with the proctoscope and from the stools themselves in these two cases resulted in good growths of Bargaen's diplococcus. The organisms gave all the characteristic morphological, cultural and fermentative reactions described by Bargaen. The isolation of the organism, however, does not prove that it is the cause of the disease. We have rather frequently found the diplococcus in the stools of normal individuals, as have other observers. On the other hand, the possibility of an etiologic relationship can scarcely be denied.

Since the etiology of ulcerative colitis is still far from being proved it is not at all surprising that there should be a large variety of treatments. Each of the two cases under discussion received entirely different types of therapy. Peculiarly enough they are equally well improved. In Case I Bargaen's antiserum (concentrated) was used. Two intramuscular injections of the serum were given daily. Beginning with 0.1 cc. the first day, the dose was then increased by 0.1 cc. for each injection, daily. On the eighth day a localized erythema developed over the injection areas. In addition to the serum the patient received a liver and iron preparation to combat the anemia. She was given 15 Gm. four times a day. The diet was one of low-residue, nonlaxative foods, high in caloric value. As was shown in the history of this case, she made very satisfactory progress. The group of cases seen at this clinic in the past year and treated with Bargaen's serum has been so small that we do not feel warranted in drawing any conclusion with regard to its efficacy. A rather significant observation has been made, however. On the third or fourth day after starting the serum the patients

cystic tumor of the right ovary were removed; in 1920, she was in a cast for seven months for correction of a spinal curvature, thought at one time to have been tuberculous. A sister had died of tuberculosis of the spine. Minor upper respiratory infections were a frequent occurrence.

During the winter of 1931-1932 she had been confined to bed three times by "influenza," characterized by fever, weakness, vomiting and, on the first occasion, by pain in the left lower quadrant of the abdomen. In March, five months before her entrance here, the third and most severe attack kept her in bed for six days, during which she vomited continuously, losing 11 pounds in weight. Convalescence was never complete. Strength remained poor, vomiting occurred not infrequently, and she gradually declined some 8 pounds further in weight. On May 30, 1932, she again had a knifelike pain in the abdomen, radiating from the left lower quadrant where it began, and a little later an old dragging discomfort in this area became intensified. Dyspnea and palpitation were present on exertion.

Two months before entrance she noticed increased pigmentation about both elbows, around the fingernails, under the knee, on the neck and in the old laparotomy scar, but interpretation was confused by recent exposure to the sun. Faintness, first apparent on arising in the morning and later during any attempt to stand, was present for one month. She required bed rest much of the day.

Physical examination showed a wan, tired, anxious woman, somewhat undernourished. Her weight of 111 pounds for a height of 5 feet 4 inches was 25 pounds below the standard and approximately that below her own normal. A brunette, her skin was, moreover, well tanned and the outline of a bathing suit was clearly distinguishable. Over the forehead, face, neck and arms there was deep freckling and in addition some more diffuse darkening; the lines of the knuckles and the skin at the bases of the nails were brownish; the areolae of the nipples and the old laparotomy scar were dark brown; there was some local patchy darkening in the right popliteal fossa. There was a little darkening of the dermal portion of the lip but nothing definite within the oral cavity. The total impression was one of slight pathologic pigmentation.

The general physical examination was otherwise negative. Her blood pressure was 88/68, pulse at rest 90 to 100, and the rectal temperature 98.4 to 100 F. Pelvic examination showed a small, tender mass in the left adnexa. Wassermann and Kahn tests on the blood were negative. Red blood cells, 3,260,000 per cubic millimeter, hemoglobin 75 per cent, and white blood cells 8850 per cubic millimeter. Urine examination negative. An x-ray showed no calcification in the adrenal regions, but a fusion of the bodies of the third and fourth lumbar vertebrae with a total obliteration of the intervertebral disk, and a fusion of the articular facets between lumbar 3 and 4.

A diagnosis of Addison's disease, left salpingo-oophoritis and healed tuberculous spondylitis was made. The patient left the hospital on August 20th and was seen again in the out-patient department on August 27th, a Saturday. She felt definitely better, was able to be up and about several hours a day, and was eating well. It was decided to postpone therapy with the precious suprarenal cortex extracts until the full extent of this spontaneous upswing could be determined. She was urged to accept an invitation to the country for convalescence.

On Sunday she felt extremely tired but ate a large dinner and was able to

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A CASE OF ADDISON'S DISEASE TREATED WITH AN EXTRACT OF THE SUPRARENAL CORTEX

THE epoch-making success of Hartman and his collaborators and of Swingle and Pfiffner in extracting from the suprarenal cortex a substance which will indefinitely prolong the life of animals deprived of their suprarenal glands is now being pursued haltingly and painfully in the difficult problem of Addison's disease in man.

The instance to follow is that of a woman treated with the commercial Swingle-Pfiffner preparation, having a potency of 8 to 10 dog units per cubic centimeter. The dog unit, as defined by Harrop, Pfiffner, Weinstein and Swingle, is the minimum daily dose per kilogram which will maintain a normal physiologic state, measured by body weight and nonprotein nitrogen or urea in the blood, in an adrenalectomized dog for seven to ten days. The greater potencies of 40 to 80 D.U. per cubic centimeter achieved in the laboratory have not as yet been obtained in large scale manufacture. Our first experience here with a cortical hormone, the cortin of Hartman and collaborators, was reported by Hartman and was essentially similar to this. No comparison between the products of these two groups is possible on our limited material.

Case I.—A female secretarial worker, aged thirty-nine, was first admitted to Billings Memorial Hospital, on the surgical service of Dr. D. B. Phemister, on August 15, 1932, complaining of weakness, gastro-intestinal irritability and pain in the left lower quadrant of the abdomen.

Her medical past had been eventful. Married at sixteen, she was divorced three years later, having had three induced abortions and supposedly acquiring gonorrhea from her husband. In 1916, at the age of twenty-three, tuberculous peritonitis was described following a laparotomy; in 1918, the appendix and a

cc., glucose 134, cholesterol 188, creatinine 1.7, CO_2 of serum 13.3 millimols per liter (normal 22-30), pH of the serum 7.33. The urine was now collectible and varied from 1770 to 3325 cc. in twenty-four hours. The rectal temperature returned to normal.

From then on there was gradual improvement until by the day of discharge on October 1st, she was comfortable while in bed, eating fairly well and able to be up in a chair an hour or so a day. Her temperature was normal, her pulse from 100 to 120. Her blood pressure ranged about 90/55. During the last ten days of her stay she was not, however, gaining weight, remaining at 102 pounds. On September 20th her blood urea nitrogen was 27.2 mg. per 100 cc., the urea clearance $\left(\frac{\text{Urine urea concentration}}{\text{Blood urea concentration}} \sqrt{\text{Urine volume per minute}} \right)$ being 9 as compared to a normal of 40 to 65. On September 26th, the blood urea nitrogen was 45.5, the urea clearance 10. On both of these days her fluid intake and excretion were perfectly normal. Her blood had improved very slightly. The red blood count being 3,600,000, the hemoglobin 60 per cent, the white blood count 9000. The ulnar paralysis was unchanged, the decubitus ulcers healing. The suprarenal cortex preparation had been gradually reduced until she was receiving approximately 15 cc. weekly, in doses usually of 5 cc. every second or third day.

She then left for her home in Nebraska, where she continued to take 15 cc. of cortical extract weekly. Her reports varied in tone. At times she was cheerful and felt well, at other times she was depressed, unable to be out of bed and suffering considerable gastro-intestinal disturbance. Saturday, December 31st, she passed rapidly again into coma and died on January 2nd. Due to the failure in securing any report from her home physician, full details of this later period are unfortunately not available to use, nor was any postmortem held.

The preceding account of a woman who had the misfortune to develop Addison's disease in that perplexing interim between therapeutic promise and therapeutic achievement presents several points of special interest:

1. In that break from chronic disability shortly before treatment was started, a convalescent trend was converted within twenty-four hours into a state precarious in the extreme, without known provocation. The likelihood of such catastrophes, especially after such minor surgical procedures as dental extractions, after administration of drugs or with infections of little importance to most people, has been reemphasized recently with abundant illustrations by Rowntree and Snell and by Harrop and Weinstein. An untreated or half-treated patient with suprarenal deficiency is hence always living under a hazard.

be up. The following day she vomited several times and passed watery stools. She was found asleep at 5.00 P. M. and at 6.00 could not be roused. At 10.30 that night (August 29, 1932) she was brought to the hospital (service of Dr. Louis Leiter) in coma, pulseless, with apical tones faintly heard at 60 per minute, breathing in a shallow, irregular manner six to ten times per minute. The blood pressure was unobtainable, rectal temperature 105 F. A half an hour following caffeine and physiologic saline containing 5 per cent glucose, hypodermically, she partially regained consciousness, and gradually improved through the night. By morning the apical heart rate was 140 per minute, the respirations 22; the pulse was only now and then obtainable, the blood pressure not at all. While cloudy mentally, she was awake and restless. The diarrhea continued. At noon 20 cc. of the suprarenal cortex extract was given, 10 each intravenously and intramuscularly. At 2.00 P. M. a few arterial beats came through at 55 mm. of mercury, and at 5.00 a blood pressure of 72/55 was obtained. She appeared brighter and more responsive and complained of a great deal of pain at the sites of injection. Five cc. more of the extract was given that evening.

The next two days found her condition stationary; she was restless and extremely hypersensitive, pulseless at times, her blood pressure varying from 48/38 to 82/52, her rectal temperature running well over 100 F., but she continued taking some fluid by mouth. The red blood count was 3,140,000, hemoglobin 55 per cent, white blood count 7400. Ten cc. of suprarenal extract was given each day. Hypodermoclysis was continued throughout.

On September 2nd, the fourth day of treatment, a peculiar set of symptoms set in. She passed again into coma. Her head was held fixed in opisthotonos, her arms and legs rigid in a semiflexed position. Her pupillary and tendon reflexes were unchanged. Babinski's sign was present on both sides, the toes remaining arched in extension after this maneuver. Any attempt to forcibly move the limbs caused expressions of pain. A lumbar puncture revealed the spinal fluid under 100 to 110 mm. of water pressure, with a normal response to jugular compression. The clear fluid had 8 polymorphonuclears and 10 red blood cells per cubic millimeter, and negative reactions to tests for globulin. A puncture the following day showed 20 lymphocytes and 2 crenated red blood cells per cubic millimeter. On culture and guinea-pig inoculation, nothing was found. Ophthalmoscopic examination was negative. An x-ray of the skull was negative. A small specimen of urine had a specific gravity of 1.012, a trace of albumin and an occasional red and white blood cell in the sediment. Throughout this day and those immediately following, her pulse was of comparatively good quality, her blood pressure from 70 to 80 systolic and from 35 to 60 diastolic. Fifteen cc. of suprarenal extract was given intramuscularly on September 2nd, and thereafter on successive days 10, 15, 10, 20 and 20 cc. Ringer's solution was substituted for saline in the hypodermoclysis on September 5th.

On September 6th, 7th and 8th, about a week after the onset of the spastic phenomena, the stiffness of the muscles relaxed, her mind cleared, and her strength improved. Decubitus ulcers had, however, developed on both heels. She remained for some time markedly hyperesthetic and exhibited hypoalgesia and weakness of the fourth and fifth fingers of the right hand, the result of an ulnar nerve injury, presumably traumatic. On September 7th, blood could at last be secured for chemical examination. The urea nitrogen was 59 mg. per 100

has never been clear how much of this failure is due to the restriction of fluid available for urine formation and to decline in the blood pressure and how much to direct impairment of the kidneys. Harrop and Weinstein have recently presented data on the capacity of the kidneys to excrete urea as measured by the blood urea clearance of Van Slyke, obtained when the patients were in sufficiently good clinical condition to make the test satisfactory, technically. In all but 1 of 7 tabulated, the urea clearance was from 22 to 52 per cent of normal, and the single exception had had no attack of acute insufficiency. Vigorous therapy with suprarenal extract in one patient failed to help matters. The results on our patient are in accord with these findings. On September 20th and 29th, twelve and twenty-one days after recovery from the crisis, her blood urea clearance was 9 and 10, respectively, as compared to a normal of 40 to 65.* Her urine output was 1400 cc. in twenty-four hours on the 20th, showed no abnormalities on several microscopical examinations during this period and she was taking fluids well and improving in general strength. Her blood pressure during this period ranged around 82/58, although unfortunately values are not available for the precise time of the test. It may be definitely stated, therefore, that impaired kidney function was not due to loss of fluid from the body, but the rôle of inadequate arterial pressure is less surely determined, as with hypotension of this degree glomerular capillary pressure may well approach the critical level for adequate filtration.

5. From the first to the tenth day of treatment, by which time she was fairly well out of danger, the patient received 145 cc. of the suprarenal hormone. Thereafter until discharge twenty-three days later she received 78.5 cc. Subsequently she took 15 cc. weekly in divided doses of 5 cc. each. It is likely that her initial recovery was secured by the large doses of cortical extract and that the improvement obtained on the ninth and tenth days was caused by increasing the daily dose from 10 to 20 cc. The occasional spontaneous recovery from such crises makes this only an assumption when based on a single instance,

* No data are available on the urea clearance of this patient before the crisis.

2. Completely unlike the known reactions of animals, Addison's crisis may be characterized by fever. Whether this is a reaction to advancing infection or a peculiar response of the heat-regulating mechanism to adrenal insufficiency, is not known, but the fever subsides with the general improvement of the patient. When first seen in coma, this woman's rectal temperature was 105 F., and it fluctuated in general thereafter with her condition. A similar phenomenon was observed twice in the patient treated here with Hartman's cortin. Rowntree and Snell have figured the chart of such a case in their monograph and have furthermore suggested that attacks of "influenza" described by patients may possibly be periods of acute adrenal failure.

3. This patient presented from the fourth to the tenth day of treatment a peculiar comatose state with generalized tonic muscular rigidity. No adequate explanation for this phenomenon was apparent, and unfortunately postmortem examinations of the brain and cord were not possible. These symptoms receded during a time in which the cortical extract was increased from 10 to 20 cc. daily and Ringer's solution was substituted for physiologic saline by hyperdermoclysis, leaving as residua positive Babinski reflexes, some subjective hyperesthesia, and a right ulnar nerve palsy attributed to trauma. (Neurological examination by Dr. D. N. Buchanan.) While such nervous symptoms as delirium and even convulsions are well known, protracted tonic states are not at least commonly seen. Simpson has recently reported tonic spasms of the entire body in a woman of fifty-one who recovered under suprarenal therapy, and Baird and Albright saw, in a woman dying of adrenal tuberculosis, spasms of the hamstrings sufficiently striking to cause them to treat the patient for tetanus. Until detailed pathologic studies of the central nervous system are available in such cases it is of course impossible to assert justly that this is solely a reaction to suprarenal insufficiency, but the subsidence under specific treatment emphasizes this possibility.

4. While the failure of the kidneys to excrete urea in severe adrenal insufficiency in both man and animals is well known, it

has never been clear how much of this failure is due to the restriction of fluid available for urine formation and to decline in the blood pressure and how much to direct impairment of the kidneys. Harrop and Weinstein have recently presented data on the capacity of the kidneys to excrete urea as measured by the blood urea clearance of Van Slyke, obtained when the patients were in sufficiently good clinical condition to make the test satisfactory, technically. In all but 1 of 7 tabulated, the urea clearance was from 22 to 52 per cent of normal, and the single exception had had no attack of acute insufficiency. Vigorous therapy with suprarenal extract in one patient failed to help matters. The results on our patient are in accord with these findings. On September 20th and 29th, twelve and twenty-one days after recovery from the crisis, her blood urea clearance was 9 and 10, respectively, as compared to a normal of 40 to 65.* Her urine output was 1400 cc. in twenty-four hours on the 20th, showed no abnormalities on several microscopical examinations during this period and she was taking fluids well and improving in general strength. Her blood pressure during this period ranged around 82/58, although unfortunately values are not available for the precise time of the test. It may be definitely stated, therefore, that impaired kidney function was not due to loss of fluid from the body, but the rôle of inadequate arterial pressure is less surely determined, as with hypotension of this degree glomerular capillary pressure may well approach the critical level for adequate filtration.

5. From the first to the tenth day of treatment, by which time she was fairly well out of danger, the patient received 145 cc. of the suprarenal hormone. Thereafter until discharge twenty-three days later she received 78.5 cc. Subsequently she took 15 cc. weekly in divided doses of 5 cc. each. It is likely that her initial recovery was secured by the large doses of cortical extract and that the improvement obtained on the ninth and tenth days was caused by increasing the daily dose from 10 to 20 cc. The occasional spontaneous recovery from such crises makes this only an assumption when based on a single instance,

* No data are available on the urea clearance of this patient before the crisis.

but this experience is so completely in accord with that of others and with our own previous case treated with Hartman's cortin that it is a fair position to take. It is, furthermore, apparent that 15 cc. weekly was an inadequate maintenance dose. On the basis of the dog unit, 30 to 40 cc. weekly would be required, assuming that the tissues of man respond equally to those of the dog and that the patient's own adrenals were producing no hormone. Her requirement would come much closer to this figure than to the amount actually used. Increasing the frequency of dose, following the plan of Hartman and his co-workers, might also have facilitated the utilization of the amount given.

Unfortunately the great expense of treatment makes it necessary to conserve the economic resources of the patient and his friends and family. Between the Scylla of inadequate treatment and the Charybdis of insolvency is a narrow channel indeed. If anyone knows of a philanthropically inclined gentleman, whose resources have survived these degenerate days, and who should chance to have Addison's disease afflict him or someone close to his heart, let him by all means point out the inestimable service that can be rendered these sufferers between now and such time as it is possible to bring this precious material within a reasonable cost of production.

In this connection it is worthwhile to pass briefly over the prospects for successful therapy in the future. We are justified in basing the heartiest hope on material which has time after time met the most rigorous tests in the experimental animal. Following the statistics of Barker and Guttman, approximately 15 per cent of Addison's disease is due to that isolated destructive disease miscalled "atrophy" and most of the remainder to tuberculosis. In only 4 of Barker's 26 cases of suprarenal tuberculosis examined at necropsy was there no active lesion elsewhere in the body, making it only about a fourth of the patients in which serious disease outside the suprarenals may be disregarded. However, the extent and activity of these other lesions is often not great, and the beneficial effect of proper substitution therapy may well be considerable. The lesion in the

TABLE OF PATIENTS TREATED THUS FAR WITH PREPARATIONS OF HARTMAN AND SWINGLE AND PEIFFNER

Author.	Number of cases.	Number of substantial initial improvement.	Number now alive.	Receiving continuous treatment.	Receiving intermittent treatment.	State of Health.		
						B ₁ .	B ₂ .	C.
Rowntree et al. (Nov., 1931).....	20	18	14	5	9	9	5	
Hartman et al. (March, 1932).....	7	6	5*	4	1	4	1	
Hartman et al. (Oct., 1932).....	7†	7	3	3	..	2	..	1
Harrop and Weinstein (April, 1932)	8	7	4	4	..	2	2	
Baird and Albright (Sept., 1932)...	2‡	2	0					
Simpson (1932).....	6	6	3	2	1 no treatment	3		
Horak (1932).....	1	1	1	..	?	1		
Benham et al. (1932).....	3	2	0					
Thompson and Whitehead (1931)...	3	3	3	2	1	1	2	
Cantor and Scott (1932).....	1	1	1	1	..	1		
Thompson and Russell (1932).....	1	1	1	1	..	1		

* Two of these five have subsequently died.

† Including our first case—only 2 under Hartman's control.

‡ Two others included in series of Harrop and Weinstein.

B₁—good condition—moderate activity.B₂—good condition—slight activity.

C—requires bed rest.

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suprarenal itself unfortunately shows little tendency to heal; what it will do when cortical hormone is provided remains to be determined. The somewhat feeble regenerative processes may of course make headway, but one may be guided by the disappointing clinical manifestations of such regeneration of the pancreas as may occur in the insulin-treated diabetic and count on little in this regard. Some variations in the function of the impaired adrenal take place however, and 9 of Rowntree's 20 patients required only intermittent therapy, but the wisdom and safety of such a plan will take time to settle.

Two questions of great practical and scientific interest await the development of our knowledge of the patient with severe adrenal destruction given adequate amounts of extract. These are: (1) Whether the functions of the adrenal cortex in man can be completely replaced by this cortical hormone as we now know it; and (2) just how vital are the functions of the adrenal medulla? It is proper to qualify with just this much reserve the great hope and confidence that all clinicians put in these brilliant results of the investigations of Hartman and his co-workers, and of Swingle and Pfiffner.

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at the apex. An electrocardiogram showed a sinus rhythm with a rate of 84 and was essentially normal. The blood pressure varied from 170 systolic and 90 diastolic to 210 systolic and 110 diastolic. The urine was normal on examination but an Olmsted test showed a decreased ability of the kidney to concentrate urine. A two-hour phenolsulphonephthalein test gave a 60 per cent return of the dye in two hours. The blood was normal, and the Kahn and Wassermann were negative. She was put upon a régime, the principal feature of which was rest, and did very well until her present entrance. In the intervening interval the blood pressure varied within essentially the same limits as those observed at her first entrance.

On Thanksgiving day the patient was especially active. During the evening, while seeing some guests off at a railway station, she suddenly developed a very severe dyspnea without any previous symptom of discomfort. This was accompanied by what she described as a terrific pounding in the chest. At the same time she was aware of a pain originating under the upper third of the sternum and radiating down the left arm to the wrist and through the chest to beneath the left scapula. The pain was not severe and gradually wore off in the course of an hour, but the dyspnea was very distressing and the source of great anxiety. She was taken in a wheel chair to the emergency room of the station where she was given nitroglycerin without any relief. After a rest there the dyspnea became a little easier and she was driven home. Here she was seen by an associate who sent her at once to the hospital in an ambulance.

When seen in her room upon entrance, the patient was sitting up in bed and stated that she could not breathe reclining. The respirations were 35 to the minute and very distressing to the patient because of their urgency. The slightest move brought on an unproductive cough. The pain had disappeared and, except for the dyspnea, she was quite comfortable. The pulse rate was 150 to the minute and regular except for occasional ventricular extrasystoles which had been more frequent when she was examined in her home. The blood pressure was 158 systolic and 105 diastolic. The rectal temperature was 98 F. Examination showed a moderate cyanosis and an edema of the lungs on both sides.

The history of the attack in this case is amply sufficient for a diagnosis of coronary thrombosis. Dr. J. B. Murphy used to tell his students, "Listen to the patient's story. Listen to what the patient tells you. He will tell you the diagnosis." In this particular case it is clear, but it is not always so clear from the patient's history. The very moderate degree of pain experienced is not at all inconsistent with a coronary thrombosis. There may be even less pain or no pain whatever. The dyspnea, appearing suddenly in a patient up and about, is significant of itself, as is any dyspnea not explained by the physical findings and history, even if it does not appear suddenly. Usually there is a fall in blood pressure either at once or early in the course of

CLINIC OF DR. N. C. GILBERT

ST. LUKE'S HOSPITAL

TREATMENT OF CORONARY THROMBOSIS

WE are showing this case not because of the rather typical history and course, but as a basis for the discussion of the treatment of coronary thrombosis. The diagnosis has been discussed previously.

I do not wish to outline any routine treatment. There are relatively few situations in medicine where a definite and pre-conceived plan of campaign is advisable. Usually there are certain therapeutic measures which should be taken promptly in each case, and others which will depend upon the course which the disease takes. The problem is very much that of a military campaign. It is a good thing to follow Wellington's example and to have a tentative plan of campaign in your mind, but one which is flexible and can be readily changed to meet or to anticipate changing conditions.

We will go over the clinical course rather briefly.

The patient is a married white woman of native stock, aged fifty-two. She is now at the end of her fourth week in the hospital. At this time there is no indication of any illness to be seen on inspection and very little indeed to be elicited on physical examination. At the time when physical findings were present, it would have been impossible to show her in the clinic. At that time we were especially desirous of securing absolute quiet.

The family history is negative. The previous history includes typhoid at the age of twenty-five, pneumonia at thirty-eight, following influenza, and a hysterectomy at forty-one because of uterine fibroids which were the cause of profuse hemorrhage. There have been two uneventful pregnancies and no miscarriages. For the past three years she has been unable to sleep at night without three pillows but there has been no edema and no definite shortness of breath.

Nine months ago the patient entered this hospital for a few days because of a mild upper respiratory infection and for observation. At this time the heart showed a moderate left ventricular hypertrophy and there was a systolic murmur

During the next week it varied from 80 to 90 and since then has varied between 70 and 80.

The respirations became easier very promptly after oxygen was started and the patient was very comfortable in half an hour, although the respiratory rate decreased only to 28. It decreased to 24 the next morning and, after varying from 24 to 28 for five days, reached a constant level of from 20 to 24.

The blood pressure fell gradually each day until the fifth day on which it was 120 systolic and 90 diastolic. It then gradually rose to vary around 145 systolic and 90 diastolic from the eighth day on.

The temperature began to rise during the night of her entrance and the next day was 100.8 F., and 101.4 F. the third day. It then gradually fell, reaching normal on the sixth day.

The edema of the lungs decreased rapidly but was still present on the morning after entrance, although very slight. It increased on the fourth day but disappeared on medication and has not reappeared.

The white blood cell count was 12,000 on the second day and 13,500 on the seventh day. Unfortunately we have not a recent count. The urine remained normal.

A friction rub appeared at the level of the third rib at the sternal margin on the third day, thirty-six hours after entrance. It was present all of that day but was gone on the next day and did not reappear.

I have gone over the findings and the course rather hurriedly in order that we may have more time for a discussion of the treatment.

There is one measure to be taken which very obviously must be a fixed feature of the plan of campaign. The patient must have absolute physical and mental rest and quiet. The patient should not make a move which can be avoided. Nothing should be done which will increase the pulse rate one beat. We would not have moved this patient to the hospital if it could possibly have been avoided. Nothing should be betrayed by look or word or action on the part of the attendants which will add to the already existing apprehension of the patient.

a coronary thrombosis, but not invariably so. Recently, at an autopsy in this hospital, an infarct of the heart muscle with consequent rupture was found in a case where the diagnosis had been somewhat doubtful. The fact that this patient had continued to have a high blood pressure had been one of the reasons for doubting the diagnosis. Shortly after this another case occurred in which we felt sure of our clinical diagnosis. In this case also the blood pressure remained high.

The patient whom we are showing was so ill and the story so typical that a diagnosis could not be avoided. But this is not always the case. Do not forget the case where the history is not typical and where the physical findings are insignificant or absent. Do not forget the patient with only a very slight pain under the sternum or in the arm or along the sternocleidomastoid muscle, or in the epigastrium, or any of the many points to which the pain is referred. Do not forget the patient with only a little dyspnea or only a moderate change in the pulse and with no edema of the lungs; the patients who stay up and about and who make light of it all themselves. True enough, it may be something else. But at least, carefully consider the possibility of a coronary thrombosis and be doubly sure that it is not present. If there is any doubt, be on the side of safety. I have very little fear of any psychological trauma resulting from being on the safe side. I would rather bear the odium of being too careful than of not being careful enough. Remember, also, that coronary thrombosis may occur in the course of various mild infections and recognize it as coronary thrombosis. Too often it is confused with the original infection.

Do not be misled by the absence of laboratory findings. To quote Dr. J. B. Murphy again, "Diagnoses are made in the cortical cells and not in the laboratory."

In this particular case a previous electrocardiogram was normal, and a tracing taken immediately after entrance showed evidence of coronary damage.

On the morning after entrance the pulse rate had fallen to 120 and remained at about that level until the fourth day, when it began to gradually fall and reached 80 on the seventh day.

it is of definite value not only for the relief of the pain, of the dyspnea and the pulmonary edema, but that it may do a great deal to lessen the degree of anatomical damage and to aid in repair. No doctor is able to determine from the subjective symptoms or the objective findings just how much or how serious is the damage which has resulted from the thrombosis. There may be very minor symptoms or findings and yet an extensive infarction may be present which may rupture. Ventricular fibrillation may occur in what are apparently mild cases or in cases which appear to be progressing favorably. It is much better in our opinion to start the use of oxygen at once, even in the very mild cases. Its use should be continued until pulse and respiration are normal and continue normal in its absence, and until findings have disappeared. I would not worry nearly as much in regard to the psychological effect of its use as I would in regard to possible increase of pathologic changes in its absence.

In this case, oxygen was administered by the nasal catheter method. It is because this simple and always available method was used that we are showing this particular patient. The nasal catheter method is not as certainly efficient as an oxygen room or an oxygen tent, but it does maintain a concentration of oxygen in the nasopharynx sufficient to be of great clinical value. The simple apparatus can always be improvised anywhere. The technic of administration is simple and the cost of administration very slight. The relief afforded more than compensates for the almost negligible discomfort and it is not as disconcerting to the patient as a tent or an oxygen room.

Lubricated rubber catheters are passed through each nostril until they touch the posterior wall of the nasopharynx or until they elicit a gag reflex. They are then withdrawn $\frac{1}{4}$ to $\frac{1}{2}$ inch so as to avoid any reflex gag or cough. The catheters should have additional small holes cut in the terminal $\frac{3}{4}$ inch so as to avoid a strong current of oxygen from a single opening impinging on the mucous membranes and causing discomfort and irritation. The catheters should be small enough to allow the patient to readily breathe through the nose with the mouth shut, as this insures a higher percentage of oxygen in the tidal air. They

The use of oxygen should be explained briefly and simply so that the patient will not consider its use as a last desperate resort but as a simple measure for the relief of symptoms and as carrying assured safety. The same applies to other measures. Just as little should be done as possible and that little done easily and quietly and naturally. Examination by the physician should be confined to only what is necessary to confirm the diagnosis and to observe progress. Visitors should be restricted but not to a point where it might arouse the apprehensions or disturb the equanimity of the patient.

The complete rest should be continued for a matter of weeks. Certainly from four to six weeks should be a minimum. In this case after four weeks of absolute bed rest, the patient returns to her home for further rest. Just how long further rest should continue is a matter of judgment in each individual case.

When this patient entered, the body temperature was slightly subnormal and the extremities were cold. She was given warm coverings and hot-water bottles were used to aid in restoring warmth. The varying degrees of shock will usually yield to rest, warmth, oxygen and time. We prefer to do just as little as we possibly can.

Under ordinary circumstances, morphine is administered at once to relieve pain, to obviate shock as far as possible, to allay the apprehension, and to insure quiet. When the pain is intense the initial dose of $\frac{1}{4}$ grain is repeated in one-half hour or less and, if necessary, a larger dose is given. If possible, we strive to avoid using a dose which might depress the respiration. In this case there was no pain on entrance, the patient was cheerful, apprehension had ceased, and she was comfortable except for the dyspnea which was relieved at once by the oxygen. Morphine is by all means the sedative of choice, but there is always a possible tendency to nausea or to constipation. In a case such as this, where it was unnecessary, it is better to avoid it. Individual judgment may dictate the use of milder sedatives in some cases.

The administration of oxygen is another measure which we feel should be undertaken routinely and at once. We feel that

tinued by gradually decreasing the flow and by beginning to give short periods of rest during the day when the catheters are removed.

The use of oxygen therapy in coronary thrombosis and the use of nasal catheters is nothing at all new. The use of the nasal catheters was described by Barach in 1929 and the use of oxygen in coronary thrombosis reported later by Barach and others. A review of oxygen therapy in general by Dr. Boothby appeared lately in the *Journal of the American Medical Association*.

I am not sure that oxygen is used as generally as it deserves to be in spite of all that has been written about it. We feel very certain that the use of oxygen has been of very great value in our cases, not only in relieving pain and dyspnea and pulmonary edema, but in reducing our mortality. We would like to think that it tended to decrease the anatomical damage and lessen future disability in those who recover. But it is to be used not only at first, or until pain is relieved, but for days and until the symptoms have subsided and pulse and respiration are normal or nearly so.

In coronary thrombosis we have an area of heart muscle which has been deprived of its normal blood supply and is receiving only a reduced blood supply from anastomosing vessels and the thebesian circulation. This blood supply may be reduced to a point incompatible with maintenance of life in the tissue or to a point where the tissue can barely survive or survive only with serious permanent damage. In other cases, because of more fortunate conditions, the blood supply is adequate to insure the life of the tissue and the recovery of the patient without any outside aid. It is unfortunate that we are not able to say whether or not this will be so in any given case. It is quite conceivable that there should be cases where the addition of even a very moderate amount of additional oxygen in the reduced blood flow to the infarcted areas might be just enough to turn the scale and make the difference between life and death.

When there is no edema of the lungs or only very slight edema, the hemoglobin of the arterial blood is very close to its

should also be as large as is possible in order to avoid too forcible a jet of oxygen. Usually 12 x 14 gauge catheter is used. When once in place the catheters are fixed in position by means of adhesive tape and connected by means of a glass Y tube to the tube leading from the tank. The catheters should be removed three or four times daily for cleansing. A nasal spray of plain oil administered while they are out may lessen the discomfort.

In an emergency, when a high pressure tank with reducing valves and gauges is not available, an ordinary low pressure tank may be used and with a large flow is better than nothing and may afford marked relief.

To obtain adequate results a high pressure tank, fitted with a reducing valve and control, should be used. The oxygen should pass through a supplementary apparatus designed to add sufficient additional moisture to the oxygen and equipped with a water gauge to measure the flow in liters per minute. The apparatus which you see here is a convenient form for use. It consists of a system of three mason jars, fitted into an easily portable frame. The oxygen passes from the tank through a reducing valve, where the rate of flow can be controlled, into the first of the jars. This jar is filled with water up to the mark indicated. The oxygen passes out through a screen near the bottom of the jar where it is broken up into fine bubbles in order to increase the surface in contact with the water, that it may carry more moisture. Unless this is done, it causes an irritating dryness in the nasopharynx. From this jar the oxygen flows into a second jar equipped with a water gauge to show the actual flow of oxygen in liters per minute. It then passes into a third empty jar in order to trap any excess water, and then to the catheters. A flow of at least 6 to 8 liters per minute should be maintained. In this way a percentage of oxygen in the nasopharynx as high as 35 to 40 can be reached. It may be necessary to reduce the flow because of discomfort from the stream of oxygen, but with two catheters this rarely occurs. As improvement continues, the flow can be reduced, to be at once raised if found insufficient. Its use is probably best discon-

enough to add to the diuretic effect and in experimental animals the same dose per kilo would have a slight vasodilator effect upon the coronaries. Novurit is supposed to be less toxic than the other mercurial diuretics and it is our impression that it may work better in the cases where we are not administering acid-base salts at the same time. In this case a moderate diuresis followed its use, the output of urine increasing from 950 to 1500 cc. for the twenty-four hours. It was sufficient to clear up the edema and it has not returned.

The use of intravenous glucose has been recommended to relieve the edema and to increase the blood sugar content. There have been very good results from its use. We have had very little experience with its use and have felt that we preferred the mercurial diuretics for the relief of the pulmonary edema. We have been a little cautious in the use of the glucose solution intravenously because of a possible reaction and because of a possible increase in blood volume following its use. The last is not necessarily a valid objection but it might be, in cases where there had been previous loss of kidney function and where the kidneys failed to react promptly to the increase in blood volume. The blood sugar under ordinary circumstances returns to normal very promptly after the intravenous glucose, and for this reason we have preferred to give our glucose by mouth in small repeated doses. This can be done in various ways agreeable to the patient. In this case we gave the old-fashioned plain hard candies, which the patient liked, but it can be given in the form of additional sweetening to the beverages, in the form of glucose itself or in various ways by mouth.

In this case there was not at any time any need of stimulation. In this matter also we have been inclined to be cautious and to avoid stimulation where possible. Where it has been necessary, we have used caffeine sodium benzoate intramuscularly because of its vasodilator effect upon the coronaries. I am not at all sure that its effect has been more than temporary or that it has really tided us over a dangerous period which we would not have passed safely without it. Such questions are difficult to answer. We feel safer if we use it in an emergency.

saturation point and only a very slight additional load of oxygen can be carried by the corpuscles. But even the 2 per cent, and possibly 4 per cent, of additional oxygen added by oxygen therapy may be of importance. However, in the usual case of coronary thrombosis there is edema of the lungs of varying degree, and the hemoglobin may be only 70 or 80 per cent saturated. A very mild cyanosis that can barely be detected has been shown by Stadie to correspond to about a 10 per cent oxygen desaturation.

In addition to the oxygen carried by the corpuscles, some oxygen is carried in simple solution in the blood plasma. Under ordinary circumstances this is only about 0.24 cc. per 100 cc. of blood as compared with the 17.4 cc. present in combination with the hemoglobin. But it increases with the partial pressure of the oxygen inspired, and with an oxygen percentage of 40 would be almost doubled. You will recall the experiment of Haldane. In this experiment a mouse placed under a jar was subjected to carbon dioxide gas until the oxygen-carrying power of the red blood corpuscles was completely lost. By raising the percentage of oxygen and the pressure as well, enough blood was carried in a simple solution in the plasma to maintain life in the mouse.

In our case the dyspnea was relieved at once by the oxygen and the edema of the lungs decreased rapidly. Some edema at the extreme base persisted. On the fourth day the edema began to increase slightly. Such an edema is a disadvantage to the patient because it increases oxygen desaturation and because it may predispose to inflammatory changes in the lung.

At the suggestion of my associate, Dr. C. A. Johnson, we have made use of salyrgen and other mercurial diuretics for the relief of the pulmonary edema in our coronary thrombosis cases, as well as in those of other origin. In this case 1 cc. of Novurit was given intramuscularly when the edema showed a tendency to increase. Novurit is a 10 per cent watery solution of an organic mercury compound to which has been added 5 per cent of theophylline, so that it contains 0.05 Gm. of theophylline. This is a relatively small dose of theophylline but

glycemia. In general, we endeavor to maintain the blood sugar at a high normal level.

If the bowels approximate normal, they are left alone. In this case nothing was done. If there is a spastic colon the usual routine of avoiding cathartics is carried out, using a heavy mineral oil or, better yet, vaseline by mouth and using a spastic colon diet with agar if necessary. If anything is necessary to aid the bowels, we prefer enemata or mild saline cathartics. We avoid strong cathartics and avoid any cathartic if we can.

When this case was first seen, there were frequent premature ventricular contractions. These were less frequent upon entrance an hour later and very shortly after admission disappeared entirely. If they had persisted, or even if a ventricular tachycardia had been present, we would have relied upon the oxygen for relief at least at first.

If a ventricular tachycardia had persisted we might have used quinidine, but not unless we thought we had to. Our experience with quinidine has not been large enough to permit of saying anything very definite. It is possible that we are over-conservative. On two or three occasions where we have had severe cardiac damage we have had untoward results with moderate dosage and have regretted its use. True enough, in each case we do not know that events would have been any different without its use but we feel that it is a cardiac depressant, and prefer to get along without its use if we can. However, other men have had excellent results with it. Dr. Levine has shown that it lessens the tendency to ventricular fibrillation and this point should be considered. Dr. Fenn and I have observed the effect of quinidine upon the coronary flow of dogs. We found no decrease in flow volume in doses corresponding to those used clinically which was not either commensurate with the fall in blood pressure or less than commensurate.

Occasionally auricular fibrillation appears at the onset of the attack. Here again we prefer to rely upon oxygen and upon time for results and so far have found this treatment satisfactory.

Heart block we have had little experience with and none

Epinephrine has been used in emergencies but we have had no real experience in its use.

This patient was given theobromine calcium salicylate in 7.5-grain tablets four times a day, beginning on the second day. We used the calcium salt because it is less apt than the other purine-base diuretics to cause nausea or other uncomfortable symptoms. We are not certain enough of its value to take any chances on unpleasant symptoms in a patient whom we are so very desirous to keep comfortable and undisturbed. I feel very certain of the value of the purine-base diuretics in many cases of angina, but in the acute stages of a coronary thrombosis their value is not so plain. Nature usually adapts its mechanism to the physiologic advantage of the organism, and it would seem reasonable to assume that the moment the thrombosis occurs there is an immediate vasodilator response in the coronaries. Nature must provide very well for an increased circulation in the anastomosing vessels if we are to judge by clinical recoveries, or by the infarcts found at autopsy in cases where there is no history indicating a coronary accident.

However, it is possible that these purine-base diuretics do maintain an increased coronary flow or do guard against a vasoconstriction. Aside from possible nausea or other symptoms, they can do no harm and I prefer to use them and to continue their use after the patient leaves the hospital.

For the first three days this patient was put upon a soft, bland diet which was gradually increased to a full general diet. Great care is taken to avoid any food which is indigestible in the patient's experience or could cause gas. Many of these patients suffer from a spastic colon and if this is present, the diet is modified to meet this condition.

If diabetes is present, the diet may be altered somewhat to meet the conditions, but the coronary thrombosis is treated first and not the diabetes. It is very undesirable to do anything which would lower the blood sugar below the optimum level. Dr. Strouse and his co-workers have reported anginal attacks occurring with low blood sugar. If insulin must be used, special care should be taken to avoid even a temporary and brief hypo-

The treatment after the acute symptoms have subsided must vary with each case. This case has been in bed four weeks and will go home to stay in bed for possibly two weeks longer, when she will be allowed to gradually increase her activities. How soon we let her up will depend entirely upon her response to exertion. I do not think that from four to six weeks is any too long for the initial period of rest.

If we knew more in regard to the factors underlying coronary thrombosis, we might do more to prevent recurrent attacks. Overwork, physical and mental fatigue, and especially infections, seem to predispose to attacks. The patient's mode of life should be modified to guard against these factors. We know nothing about the advantages of any medication. We have been using the purine diuretics but we do not really know that they are of value. We have thought that some patients after the attack did better with acid-base salts, as ammonium nitrate, or with a neutral ash diet and acid-base salts. But they might have done equally well with no medication.

It is very difficult to evaluate any treatment except absolute rest, which is certainly essential, and oxygen, which is of great aid.

recently. We would prefer to rely upon the effect of the oxygen and again upon time. When it persists, we would prefer to use one of the theobromine or theophylline salts first. In three cases of Stokes-Adams syndrome not associated with coronary thrombosis theobromine gave especially good results. If the block persists, barium chloride can be tried. Small, repeated doses of epinephrine have been used.

This patient had been given nitroglycerin when the attack first appeared. We do not believe that nitroglycerin should be used in coronary thrombosis. We have seen syncope follow its use and Prodger and Ayman have recently reported harmful effects.

I can see no reason why digitalis should be used in coronary thrombosis under ordinary circumstances and I can see several why it should not. We would not wish to use it for its effect upon stimulus production for, if it did slow the heart, we are not sure that it would not decrease the minute volume. We certainly do not wish to use it for its effect on conductivity, and its effect on irritability we are most anxious to avoid. In poisonous doses, digitalis can bring on ventricular tachycardia and ventricular fibrillation. We do not really know that digitalis does increase contractility in the ventricular muscle and, while I think it does, I am not sure that we would wish it to and we certainly do not wish to increase intraventricular pressure in a heart when there is an infarct present in the ventricular muscle. We likewise do not know that we wish to increase tonus, for again the minute volume might be decreased and in addition the increased length of fiber may be an advantage. Unless we are very sure that we are aiding nature, we had best leave her to her own devices which are very apt to be for the conservation of the organism.

In addition, Dr. Fenn and I think that we have both clinical and experimental evidence that digitalis may cause a vasoconstriction of the coronaries, something which we are most anxious to avoid.

If an auricular fibrillation should appear and persist with resulting passive congestion, digitalis might have to be used.

two days before it becomes infective, the infectivity lasting about seventy-five days.²

The African type of sleeping sickness was the only one generally known by this name until 1916, and is merely mentioned to avoid confusion, as it is in no way related to lethargic encephalitis.

Epidemic lethargic encephalitis, or nona, was first recognized in this country about 1918, but there had been many outbreaks recorded throughout the civilized world before this date. While this disease has become endemic in all countries, there has never appeared an epidemic of large proportion in this country until the present one in St. Louis. A historical review of recorded epidemics of lethargic encephalitis is interesting, the data of these epidemics are, to say the least, tragic, because of the startling mortality rates and the recrudescence of the epidemics.

Japan, until 1929, had thirteen epidemics, the explosive nature of which, in widely distributed areas, led the Japanese to believe that they rained from heaven; but if one is to blame it upon the supernatural, I would be more inclined to believe that it sprouted from hell. The older history of encephalitis is, of course, obscure, and the data concerning it of little help.

That these epidemics followed pandemics of influenza is not admitted by all observers. Beckman³ believes that most investigators no longer recognize any connection between influenza and this disease, while Zentay⁴ says, "One fact seems to be clear that the pandemics of influenza which occurred about every thirty years had, as a rule, been followed by epidemics of large proportions." He also states that the epidemic following the influenza one of 1889 to 1891, known under the Italian name of nona, appears to have been identical with the disease observed before, during, and after the influenzal pandemic of 1917-1919.

Reports of lethargic encephalitis in Vienna came from Economo, in 1916-1917; also from Cruchet in France. Cruchet's reports were questioned, however, by Economo. Since that period lethargic encephalitis has been endemic over the entire world. The total number of cases being reported in

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ST. LUKE'S AND CHILDREN'S HOSPITAL

EPIDEMIC ENCEPHALITIS LETHARGICA

With Report of the St. Louis Epidemic of 1933

THE appellation "sleeping sickness" is as incorrect a name for lethargic encephalitis as infantile paralysis is for poliomyelitis. Nevertheless the name will cling because of its popular appeal. The term "sleeping sickness" has been given to two distinct diseases: The African sleeping sickness and lethargic encephalitis, endemic and epidemic. The African disease, or trypanosomiasis is an infectious one, caused by a known organism, the trypanosome, which is prevalent in South Africa and also South America. The mortality rate of trypanosomiasis is about 100 per cent. When the trypanosome enters the central nervous system there are no recoveries. The organism is found both in the blood and the spinal fluid of the patient. The African disease is transmitted by the tsetse fly whose habitat is the shores of the inland waterways. The *Trypanosoma gambiense* and the *T. rhodesiense* are the active agents in Africa; and the *T. cruzi* in South America.¹ These organisms are introduced into the body by the bite of the flies—the *Glossina palpalis* and the *G. morsitans*. These flies feed upon the blood of crocodiles, antelopes, and other wild animals. The trypanosome undergoes metamorphosis in the fly, which takes about thirty-

There is a record of an acute type of encephalitis in the fall of 1919, and in the winter of 1920 in Spokane, Washington, about 100 cases were reported. In Indianapolis a curious epidemic is reported by Kempf in 1930-1931-1932, which they called meningo-encephalopathy.

A recent paper by Stout and Karnosh describing a thorough study of 28 cases of acute disseminated encephalomyelitis occurring from June, 1932, to March, 1933, shows the present status of the cases to be as follows:

Recovered	10
Convalescing	3
Showing residual features	6
Relapse	5
Dead	3
Unknown	1

Residual features occurred in 20.5 per cent and about the same number had relapses, while 35 per cent recovered. Kempf in his discussion says there were similarities in the 200 cases during the Indianapolis epidemic. Kempf's cases were preceded by acute infection of the upper respiratory tract. In all the acute cases the cerebral symptoms overshadowed the spinal symptoms, and after a two years' survey, Kempf states none of the sequelae of epidemic encephalitis were seen, and no permanent damage to the nervous system was noted. The cases of Drs. Stout and Karnosh all had a predominance of spinal symptoms, while those of Dr. Kempf exhibited the cerebral type.

Dr. Chicote, a former intern at St. Luke's and Children's Hospitals, told me that in 1922-1923 while he was interning in the Manila General Hospital, they had a small epidemic, the handful of cases admitted to the hospital having a 100 per cent mortality rate. It is quite evident to me that epidemic encephalitis is gaining throughout the world, and that we may expect, unless we are fortunate enough in finding methods to counteract it, recrudescence of these epidemics in one of its various forms.

A present classification which seems acceptable would be the

any large country, exclusive of epidemics, would be not more than 100 annually. The oldest type, of which there are many, is probably that of the Japanese, which scientists designate as Type A lethargic encephalitis; we are speaking now of the epidemic form, the first epidemic in Japan was in 1871, the second in 1873, in which the mortality was 80 to 90 per cent, both of these epidemics occurred in the early fall. The next one occurred in 1903, from August to November; again in 1907, from August to November, and during 1909 in September. The clinical picture at this time was diagnosed as "meningeal." The next epidemic occurred from August to October of 1912 and 1916. The above eruptions all had high mortality rates and affected mainly older people. The one in 1916 had a mortality rate of 61.5 per cent; in the epidemic of 1917 younger people were attacked, but this epidemic had a low mortality rate, only 10 per cent. In 1919, during the summer and early fall epidemic, it was decided definitely that they were dealing with an encephalitis of a special kind. The 1924 epidemic is the largest one recorded, the reported cases being 7000, with a death rate of 60 per cent, the age distribution was such that 66 per cent of the people were over forty years of age. In 1925 and 1929 there were two more minor epidemics, although in the summer of 1929 there were 2000 cases, with a death rate of 65 per cent. The inference drawn by the Japanese from the reported outbreaks with which they were dealing was that a different form of the Economo type of encephalitis was developing, which they classified as Type B to distinguish it from the Economo or Type A; also differentiating from the so-called "European" form. In the summer and fall of 1913, again in 1918, Australia had an epidemic which appeared suddenly, and was known as mysterious or X disease, a few hundred cases were reported, but with a death rate of 70 per cent. In this epidemic half the patients were under five years of age. The clinical picture described is much like the Japanese Type B encephalitis lethargica. Australia was visited by a smaller epidemic in 1925. European countries have been free from any epidemics of encephalitis up to this date.

ranging from 50 to 100 cells although 1100 have been noted in the first tap; in some positive cases the cell count was normal, cell counts may show 90 per cent lymphocytes.

Eschenbrenner⁵ states that as the epidemic proceeds, the cell counts become much higher than in the earlier cases. The globulin is slightly increased; spinal fluid cultures and spinal Wassermann reactions have been negative and the colloidal gold curves normal; the quantitative sugar estimation varies from 50 to 80 mg. The blood chemistry has been found to be normal except in cases of uremia and diabetes, which have developed in the aged. The blood picture to date is that of an acute systemic infection, the average white count varies from 8000 to 14,500; Shilling differential counts have shown a marked shift to the left with 10 to 20 per cent stab cells. The acute case presents a picture of imbecility, but one is astounded by the quick recoveries that occur within five or six days. The temperature approaches normal; the spinal cell count is gradually reduced; and the Shilling blood count returns to normal. The tremors of the tongue, face and hands disappear within two weeks, and the patient becomes apparently normal.

While it is early in the epidemic, the 500 reported cases at the time of my visit to St. Louis had shown no sequela; and there have been no reported recurrences; most of the deaths are in the aged group where bronchopneumonia and uremia develop. Bronchopneumonia is a frequent fatal termination. Cough has not been noted thus far. Ninety-four per cent of the deaths in the isolation hospital occurred in those over forty-five years of age. The mortality rate up to September 9th was 14 per cent.

The few postmortem examinations that were reported showed that the disease was a systemic one. The lungs presented the picture that was presented after the deaths during the influenza epidemics—soggy red lung, occasionally hemorrhagic kidneys and a wet brain.

Symptoms.—Classification of symptoms. At present it is possible to give only an approximate value as to their comparative occurrence, as you understand the data of the present epidemic are still in the process of tabulation and study.

Economo type or Japanese Type A; Type B, Japanese form; Australian form; St. Louis form.⁴

The St. Louis Epidemic.—The epidemic of encephalitis lethargica that exploded in St. Louis and its environs in July of this year is unique in medical history in this country. It is generally agreed that the St. Louis epidemic is similar to what is known as Japanese Type B encephalitis lethargica. The symptom complex of the St. Louis disease is quite different from the endemic Type A or Economo encephalitis, inasmuch as there is no involvement of the cranial nerves, and up to the present time, no sequela. The disease is of short duration, which stamps this outbreak either as a new disease or a modification of the Japanese Type B.

The symptomatology of the St. Louis cases seems to fit more closely with Dr. Kempf's cases, except that few of them were preceded by upper respiratory infections.

The onset is sudden, with a chill or chilliness and headache, which is not always definitely localized; the fever is high, 102–106 F., average about 103 F.; toxemia, of course, is evident. Convulsions are rare; the neck is stiff; there is a positive Brudzinski; drowsiness or stupor occurs in the majority of cases; there is occasionally restlessness, irritability, or delirium; vomiting is not a constant symptom. Constipation is obstinate in all cases; the abdominal reflexes are usually absent, and there is a positive Kernig, mental retardation; dullness with disorientation as to time and place is almost a constant symptom. Occasionally there is aphasia, speech is slurred and there is a tremor of the tongue and lips, and occasionally of the facial muscles on attempted speech, and gross tremors of the hand. Dysphagia is not common, but has been noted. There has been no ophthalmoplegia. The nose and throat symptoms are not marked. Photophobia is noted in many cases. Spasticity of arms was seen in a number of cases.

Himpelman lays stress upon a diffuse injection of the throat but I cannot say that this is any more common than in any other acute infectious disease. The spinal fluid is definitely under pressure, but clear; the cell count is high and variable,

On the chart those symptoms marked were noted; you will see that there is absence of cranial nerve involvement in nearly all the cases, but that the encephalitic signs are nearly all present, with the exception of opisthotonos, diplopia and nystagmus.

In the endemic type, as in the cases studied by Stout and Karnosh, the cranial nerve involvement, diplopia and nystagmus are frequent occurrences, as were paralysis in 24 cases and cranial nerve involvement in 16 of the 28 cases. While there is some similarity, the epidemic of the St. Louis type is quite different, and one would hesitate to make a diagnosis of lethargic encephalitis without cranial nerve involvement which we have always thought was essential to diagnosis. The variations of symptoms in epidemic forms of diseases attacking the central nervous system are marked, but apparently each epidemic, while seemingly unrelated, has many constant findings which stamp it as a modification of encephalitis lethargica. The absolute absence of bacterial findings is common to both endemic and epidemic types. The climatic conditions in nearly all the epidemics recorded have been the same: hot, dry, late summers and fall. This has been true also of epidemic poliomyelitis and it was thought at first that the symptomatology in the St. Louis epidemic might be a superior poliomyelitis. Epidemiologically the spread in St. Louis resembles the spread of poliomyelitis in Philadelphia, but there are no cases of paralysis in this epidemic. The degree of infectiousness is probably that of poliomyelitis. No contacts have developed the disease and only in a few instances is there more than one case in one family. Most of the deaths reported so far have been from bronchopneumonia, and uremia occurring in the upper age scale. A few cases complained of dysphagia, but none to a point of paralysis. Ophthalmoplegia has not been found up to the present moment. This epidemic type of disease affecting the central nervous system stands midway between the epidemics of Japan and those studied by Economo and the later epidemics of the Japanese classified as Type B, but is more closely related to those described by Kempf.

Sensory manifestations:

- x Pains in legs.
- x Pains in other parts of body.
- x Hypesthesia.
- x Hyperesthesia.
- x Anesthesia.
- x Numbness.
- Other paresthesias.
- Girdle sensations.
- Astereognosis.

Motor disturbances:

- x Weakness subjective.
- Paralysis or paresis of extremities.
 - x Spastic.
 - Flaccid becoming spastic.
 - Flaccid with recovery.

x Disturbance of sphincter control.

Cranial nerve involvement:

- II.
- III.
- V.
- VI.
- VII.
- Facial diplegia.
- VIII.
- IX and X.
- XII.

Encephalitic signs:

- xxxxx Headache.
- x Nausea.
- x Vomiting.
- xxxxx Kernig's.
- xxxxxx Rigid neck.
- Opisthotonos.
- x Photophobia.
- xxxxx Pleocytosis in spinal fluid.
- Diplopia.
- Nystagmus.
- x Blurred vision.
- Insomnia.
- xxxxx Drowsiness.
- xxx Stupor.
- x Depressed.
- xxxx Confused.
- x Irrational, delirious.
- x Maniacal.
- x Receptive aspasia.
- x Memory defect.

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Treatment.—As to therapy, little or nothing has been accomplished as to cure and prevention. The infecting organism or virus has not been discovered, therefore a specific is not obtainable. Convalescent serum logically should be of value, but the epidemic in this country found us unprepared with any such serum.

This hospital managed to secure some convalescent serum recently which we would unquestionably try in the event of cases coming under our control.

The United States Public Health Bureaus are now studying the question of the insect as a possible carrier, as well as the sewage, water, food and milk supply.

Dr. Margaret Smith, of Washington University, found some inclusion bodies which might indicate a virus as the active agent, but up until this date definite proof is wanting.

Let us hope that from the study of the St. Louis epidemic may arise some definite means of combating this new attack upon our nervous system.

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DISCUSSION BY DR. W. LAWRENCE HICKS

Study of 64 cases of encephalitis which came under my observation between 1919 and 1932.

A large percentage of cases give definite history of recent influenzal colds usually light in character, frequently not seen by a physician; 75 per cent of my cases give a positive history of this kind.

The general symptoms of encephalitis and their sequelae

occur from a few weeks to three years after an attack of influenza. Early the patient complains of a diplopia and headache, later vertigo and some visual disturbance with photophobia, exhaustion, with general and localized paresthesia and weakness, no actual paralysis as a rule, trembling and incoordination of groups of muscles, *with marked insomnia* sometimes for days followed by a lethargic condition from which this illness derives its name; this period lasts from three weeks to months. Except just prior to death there is no true coma present. Early the temperature ranges from 99 to 101 F. and later from 103 to 105 F., with comparative increases in the pulse rate, no gross change in the respiration. Frequently the chest shows evidence of râles, but no gross bronchitis.

The age of the patients was from sixteen to fifty. The early neurological findings consist of a weakness of one of the ocular muscles, some falling off of the visual acuity, with photophobia, slight changes of the reflexes in comparison to the two sides. Later a positive Babinski, a positive Kernig, some rigidity of the neck muscles and marked mental confusion, disorientation, with a peculiar idiotic facial expression; rarely convulsions.

Serological findings early are frequently negative for the first three to five days, later the spinal fluid is found to have increased pressure, clear fluid, increase (10 to 1000) in cell count, plus globulin, and negative Wassermann and culture. The blood picture shows evidence of similar findings found in general systemic infections.

Most of my cases had distressing sequelae, marked incoordination, in fact almost helplessness and the so-called "paralysis agitans complex" characterized by a masklike face, drooling, festination gait, muscular slowness, marked weakness of muscles and idiotic appearance of the face with slowness of cerebration. This is the worst of the sequelae and occurs in young people (as young as sixteen years of age) and is incurable.

DISCUSSION BY DR. C. S. RAUE

The name "encephalitis" has come into usage as a generic term to designate a group of cerebral disturbances with certain

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The general symptoms of encephalitis and their sequelae

The characteristic symptoms of this variety are paralyses without tremor following upon a febrile attack of vague symptoms probably erroneously thought to be influenzal in origin. The facial expression is masklike and the voice is monotonous. There is more or less mental deterioration. The limb and trunk muscles are rigid and the gait and attitude are identical with that observed in cases of paralysis agitans although the characteristic tremor is lacking.

Postinfectious Encephalitis.—The most important members of this group are the cases of encephalitis occurring after vaccination and the cases occasionally developing after an attack of measles or varicella. I have observed several such cases occurring as a complication or sequel to these diseases but I have no personal experience with it as a complication of mumps, although such cases have been reported.

Postvaccinal encephalitis is of especial interest to the pediatricist, for obvious reasons. The postvaccinal type is a disseminated encephalomyelitis. Symptoms develop ten days to two weeks after a primary vaccination, usually in children over six years old. It is rarely observed with a primary vaccination in infancy. The symptoms are headache, vomiting, fever and drowsiness. There is associated stiffness of the neck, muscular rigidity and twitching. Paralysis of the legs and loss of sphincter control may develop. When trismus and convulsions occur these cases are frequently mistaken for tetanus.

Recently I have seen 2 cases of encephalitis which followed measles. The symptoms developed ten days after the appearance of the rash. The chief symptoms were a gradually developing stupor with paralysis of the extremities. There was no ocular disturbance but there was difficulty in swallowing. The power of speech was entirely lost for a time. In one case there was only a slight fever while in the other the onset was ushered in with vomiting, fever, paralysis of the legs and retention of urine. This child also had convulsions. Convalescence was slow but no sequelae followed in either case.

common psychic and neurological manifestations. While there is a general similarity in the clinical course of these cases, still we have no definite knowledge of their etiology or epidemiology. Consequently we are not in a position to classify and diagnose them with the same facility and accuracy with which we can deal with the various clinical types of meningitis, for example.

No confusion between epidemic cerebrospinal meningitis and tubercular meningitis could possibly exist. The etiology of cerebrospinal meningitis is definitely known and it is characterized by the presence of an associated blood-stream infection. Blood cultures are positive in a large percentage of cases. In common with poliomyelitis and encephalitis the infection is supposed to occur primarily in the upper respiratory tract although the respiratory symptoms are usually of a minor nature.

Tubercular meningitis has a symptomatology as characteristic and distinct as that of cerebrospinal meningitis. It was formerly believed that the meninges were infected by the dissemination of the tubercle bacillus through the blood stream; however Rich and McCordock believe that infection results from the breaking down of a cerebral focus with discharge of the bacilli directly into the cerebrospinal fluid. They claim that it is impossible to set up a tubercular infection of the meninges by way of the blood stream.

In poliomyelitis cerebral symptoms frequently occur which are due to an associated encephalitis. On the other hand, certain cases of encephalitis present spinal symptoms identical with those observed in poliomyelitis. For this reason the generic term *meningomyeloencephalitis* has been suggested as a label for this clinical group of acute infections of the nervous system.

Epidemic encephalitis is typically represented by the lethargic, ophthalmoplegic type and also by the parkinsonian type. In these the brainstem, that is the basal ganglia, midbrain and pons, are mainly affected. In the cases developing the parkinsonian syndrome there are degenerative changes in the lenticular nucleus (globus pallidus).

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Postvaccinal encephalitis is of especial interest to the pediatricist, for obvious reasons. The postvaccinal type is a disseminated encephalomyelitis. Symptoms develop ten days to two weeks after a primary vaccination, usually in children over six years old. It is rarely observed with a primary vaccination in infancy. The symptoms are headache, vomiting, fever and drowsiness. There is associated stiffness of the neck, muscular rigidity and twitching. Paralysis of the legs and loss of sphincter control may develop. When trismus and convulsions occur these cases are frequently mistaken for tetanus.

Recently I have seen 2 cases of encephalitis which followed measles. The symptoms developed ten days after the appearance of the rash. The chief symptoms were a gradually developing stupor with paralysis of the extremities. There was no ocular disturbance but there was difficulty in swallowing. The power of speech was entirely lost for a time. In one case there was only a slight fever while in the other the onset was ushered in with vomiting, fever, paralysis of the legs and retention of urine. This child also had convulsions. Convalescence was slow but no sequelae followed in either case.

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THE DIAGNOSIS OF HEMOLYTIC ICTERO-ANEMIA IN
AN APLASTIC PHASE

HEMOLYTIC ictero-anemia is a syndrome several of whose symptoms are so striking and constant as almost to be considered necessary for the diagnosis of this condition. It is true of hemolytic ictero-anemia just as it is of all conditions with such outstanding and pathognomonic symptoms that the presence of the usual symptom picture makes the diagnosis easy but that there is danger that the absence of one or more of these classical symptoms will be too readily accepted as excluding this diagnosis. Too much emphasis is given to the individual symptoms and not enough to the history and progress of the disease and to the picture as a whole. It is the old story of not being able to see the woods for the trees.

In hemolytic ictero-anemia, the characteristic findings include: An increase of bile pigments in the blood, but not in the urine, jaundice, increased fragility of the erythrocytes, splenomegaly, anemia, increase in erythropoiesis with marked increase of reticulocytes in the blood, febrile exacerbations and often a familial occurrence. Combined these symptoms form an unmistakable picture and unfortunately it is commonly believed that every patient presents the entire syndrome—the fact is that many exceptions occur.

One might, it is true, anticipate the entire picture, for the various items are obviously interrelated. Nevertheless the literature contains instances reported where this disease has unquestionably existed in the absence of one or several of the usual characteristic findings. Thus, as will be discussed later,

the literature contains acceptable case reports in which there was no lessening of the resistance of the red cells to hemolysis by hypotonic salt solution; other instances where there was no yellowness of the skin and even a rare instance where the usual high percentage of immature red blood cells was absent from the blood. The case which is to be presented is an example of this latter type and illustrates beautifully the difficulties of diagnosis of this usually easily diagnosed disease when the case is atypical.

In the case to be presented the diagnosis at one time was disguised through the demonstration of an obstructive jaundice; at another time by the finding of a normal resistance test and finally the diagnosis was made in the face of a distinctly aplastic blood picture. This demands a little discussion before presenting the patient.

The classical picture of hemolytic ictero-anemia includes the presence in the blood of many young red cells. This has been recognized for many years and forms one part of the usual picture of the disease. The explanation of the disease is usually that there is an overproduction of weak red cells which are rapidly destroyed, particularly in the spleen. The literature contains two different views, one that the spleen is overactive and the anemia results from excessive hemolysis of red cells with secondary bone marrow hyperplasia growing to maintain a normal red cell count. The other view places the initial fault in the red cell with resulting excessive hemolysis and a tendency to anemia which is again met by bone marrow activity.

On the side of the primary weakness of the red cells are enlisted Widal, Vaquez and many others; while on the side of the exaggerated hemolytic activity of the spleen are Minkowski, Chauffard, Banti and others. Krumbhaar¹ states that "according to the former view the congenitally weak cells are destroyed in excessive numbers and taken up by the spodogenous spleen and other organs of the hemolytopoietic system. This theory, however, does not take sufficient account of the great clinical improvement that follows splenectomy." "Against the primary hemolytic rôle of the spleen which must necessarily include

¹ Krumbhaar, E. B.: Osler's Modern Medicine, Vol. 5, p. 176.

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One might, it is true, anticipate the entire picture, for the various items are obviously interrelated. Nevertheless the literature contains instances reported where this disease has unquestionably existed in the absence of one or several of the usual characteristic findings. Thus, as will be discussed later,

jaundice are followed by an increase of these elements although the anemia does not necessarily increase."

Very high figures have been reported. Baty¹ has reported a case of the "congenital" form of hemolytic ictero-anemia which showed an unusually high number of reticulocytes, up to 92 per cent over a long period of observation. In this case the reticulocyte count was still high (30-70 per cent) two years after splenectomy. Reynolds² has recorded 95 per cent reticulocytes.

On the other hand, it has long been recognized that very rarely a patient with hemolytic ictero-anemia may enter an aplastic phase with failure of erythrogenesis, increasing anemia and disappearance of young red cells from the peripheral blood. Banti³ was the first to report such a case. He concluded that the bone marrow was depressed by a toxin liberated by the spleen. Splenectomy was followed by renewed red blood cell formation. Banti believed that removal of the spleen removed the "principal instrument of pathologic hemolysis."

Very little mention has been made in systems, text-books or current literature of the possibility of a failure of erythrogenesis with increasing anemia and an absence of reticulocytes in the blood picture. For example, Naegeli, Piney, Krumbhaar,⁴ Sturgis⁵ do not comment on this possibility. Meinertz⁶ does emphasize the variability in the symptomatology of this disease and states that any one symptom may fail, but he does not specifically refer to a failure of the usually active production of red blood cells.

Finally, it may be worth mentioning that Banti believed that failure of erythrogenesis was due to a hypothetical toxin produced by the spleen; today we are more inclined to explain

¹ Baty, J. M.: *Am. Jour. Med. Sci.*, 1930, 179, 546.

² Reynolds, G. P.: *Am. Jour. Med. Sci.*, 179, 549.

³ Banti, G.: *Lo Sperimentale*, 1913, 67, 323.

⁴ Krumbhaar, E. B.: In Cecil's *Textbook of Medicine*, 2d ed., Philadelphia, W. B. Saunders Company, 1931, p. 1224.

⁵ Sturgis, C. C.: In *Musser's Internal Medicine*, Philadelphia, Lea and Febiger, 1932, p. 898.

⁶ Meinertz, J.: *Med. Klin.*, 1933, 29, 73.

Bottazzi's hemocatatonic theory (that of preparing the red cells for destruction) is the fact that in many cases increased fragility of the erythrocytes persists after splenectomy has produced a virtual cure in every other respect. Also there is no satisfactory evidence to show that the spleens of such cases contain hemolysins."

In the older literature, the tendency was to explain the disease upon the spleen but of late the emphasis has more and more placed the primary fault in the red blood cells. Naegeli,¹ for example, grants the spleen only secondary importance and stresses the constitutional factor exhibited in the abnormal red cells.

Whatever the mechanism at work there results very regularly an increased activity of erythropoiesis in the bone marrow with the appearance of greatly increased percentages of immature red cells, the so-called "reticulocytes."

Naegeli states that this appearance of young cells is not pathognomonic of this disease but that there is scarcely any other anemia in which there occurs a persistence of such a high percentage of reticulocytes. In the face of this finding, it is impossible to maintain that failure of the bone marrow in the production of red cells is the cause of the disease. Also he points out that autopsy findings support this view.

Piney² states that the reticulocytes may fall as low as 2 per cent or rise as high as 30 per cent, but he continues "it can definitely be stated that, during periods of marked anemia in these patients, the number of reticulated corpuscles is high, but there is, nevertheless, no striking relationship between the number of these elements and the degree of anemia, as is shown in some cases with large numbers of these corpuscles and practically no anemia at all. It seems to me, however, that there is a close relationship between the amount of hemolysis and the number of vitally stainable corpuscles; periods of intenser

¹ Naegeli, O.: *Blutkrankheiten und Blutdiagnostik*, 5th ed., Berlin, Springer, 1931, p. 295.

² Piney, A.: *Recent Advances in Hematology*, Philadelphia, P. Blakiston's Son & Co., 3d ed., 1931, p. 292.

TABLE I

Date.	R.B.C.	Hb.	Neutro- phils.	Lympho- cytes.	Mono- cytes.	Eosino- phils.	Baso- phils.	Myelo- cytes.	Nucleated red cells.	Reticulo- cytes.	Platelets.	Hemolysis in NaCl.	
												Begins.	Complete.
9/10/24	3,150,000	56	62.5	32.5	3.5	1	0.5	0.450	0.350
9/15/24	62.5	32.5	4	0.420	0.340
9/19/24	85	68	27	2	..	1	216,000	0.525	0.425
9/14/26	4,750,000	69	28	188,000	0.420	0.300
9/17/26	14,000	400,000
9/19/27	Normal	58
4/1/31	4,180,000	65	64	36
3/27/32	2,510,000	35	35	53	12
3/30/32	1,780,000	34
3/31/32	1,600,000	34	66	25	4	2	1	2	"Very occ."	?	0.525
3/31/32	Transfusion, 500 cc.	38
4/1/32	2,700,000	40
4/2/32	Transfusion, 475 cc.
4/4/32	Transfusion, 475 cc.	35
4/6/32	2,900,000	40	51	42	3	1	1	2	2 per 100 W.B.C.	19.8
4/7/32	3,200,000	48	62	32	3	3	..	27
4/9/32	3,400,000	55	73	19	5	1	..	2	..	18.7
4/11/32	3,500,000	72	66	30	4	27
4/12/32	3,700,000	74	25.7
4/16/32	4,400,000	79	69	25	4	2	9.7	..	?	0.475
4/25/32	4,100,000	73	63	26	5	6	18
4/27/32	4,000,000	72	69	24	4	3	14.4	224,000
4/28/32	Splenectomy Transfusion, 250 cc.
4/29/32	4,800,000	88	11	544,000
5/2/32	4,700,000	89	70	16	1	8	1,600,000	0.525	0.400
5/9/32	5,000,000	96	79	11	0	3	928,000
5/13/32	5,400,000	96	79	15	5	1	576,000
6/3/32	5,800,000	101	57	30	6	7	1.2

bone marrow failure upon an exhaustion incident to the prolonged and excessive demands made upon that function to compensate for the excessive and premature destruction of the red cells.

Case Report.—E. S., male, eighteen years of age. The patient had been ill since the age of six and had been suspected on several occasions of having hemolytic ictero-anemia but because of the absence of one or other of the classical symptoms this diagnosis had never been accepted in the past. On one occasion, the jaundice was believed to have been obstructive as a result of a statement that the stools were pale in color. On another occasion a faultily performed red cell resistance test argued against the acceptance of the diagnosis of hemolytic ictero-anemia.

The first attack of jaundice followed an attack of diphtheria at the age of six. This jaundice lasted for three weeks. Annually during his seventh, eighth and ninth years, the child had several attacks of jaundice. At the age of nine an enlarged spleen was observed, but the record states that blood counts at that time did not give a diagnosis. He was seen by prominent physicians at the age of ten, at the age of twelve and almost annually from then on. Such blood counts as are available from these examinations are given in the Table I. In 1926, the diagnosis of chronic cholecystitis and cholangitis was made. In 1931, the diagnosis of chronic obstructive jaundice due to cholelithiasis or cholangitis was made. Throughout his life his health has improved between attacks of jaundice, but at no time has he been what would be called a healthy child. He was fairly well for a year prior to the present acute attack.

On March 20, 1932, fever developed and four days before being seen his temperature was 104 F. On March 27th, a blood count was taken and an extreme anemia discovered. With this illness he was far less yellow than in former attacks, but there was a slightly muddy color to the skin. He was admitted to the Hospital of the University of Pennsylvania on March 30, 1932. An examination revealed pallor, puffiness of the face, systolic murmurs at the pulmonic and mitral areas, a definitely enlarged spleen and slightly enlarged liver. The table shows the blood examinations and records the transfusions. The coagulation time, bleeding time, and clot retraction had been recorded on several instances and always within normal limits. Patient continued ill until April 8th when simultaneously he showed marked subjective improvement and his blood picture revealed the appearance of an increased number of reticulocytes. From then on his improvement was rapid. He was allowed to leave the hospital on April 11th, being urged to rest at home for two weeks and then have splenectomy.

Splenectomy was performed on April 28th by Dr. George P. Muller. The spleen measured 10 inches by 5 inches and was adherent retroperitoneally. This increased the difficulties of the operation, but the patient's condition continued good throughout. The transfusion of 250 cc. of citrated blood was given before the patient left the operating room. During the operation the gallbladder was examined and no stones were found in it or in the common duct. The liver was apparently absolutely normal. Stomach appeared normal except for a slightly hypertrophic pyloric sphincter. Following the splenectomy the patient's

fidence can be placed in it. The test seems easy of performance, but there are unsuspected pitfalls of which the most important is the accuracy of the solutions. It takes very little evaporation to increase the strength of the solution and destroy the value of the test. Such change as occurs from evaporation tends to bring the results more near to the normal range. The only safe method (unless one is absolutely sure of one's solution) is always to set up a normal control at the same time.

Also there is evidence in the literature that the hemolytic resistance of the cells varies at times. Baty¹ reports that in his patient the fragility was normal on all but a few occasions—at such times the hemolysis commenced in sodium chloride solution 0.68 per cent and was complete at 0.52 per cent. In other words, the test must be carefully performed and intelligently interpreted.

In our patient some hemolysis occurred in the strongest salt solution employed. In the table, therefore, question marks are placed to show this uncertainty.

We have already discussed the rare occurrence of an absence of active red cell production in hemolytic ictero-anemia. This was the picture in our patient in the severe attack of "deglobulization" of March, 1932. Whether this whole attack was merely part of his disease or whether some intercurrent infection was present it is difficult to say for fever is the rule in such periods of increased hemolysis. At any rate the blood picture with hemoglobin 34 per cent; red blood cells 1,600,000 and only a very occasional reticulocyte was so atypical of hemolytic ictero-anemia that it was bound to raise a suspicion of primary aplastic or some other type of aplastic anemia.

The prompt appearance of reticulocytes up to 27 per cent after the transfusion set these doubts at rest.

Once the entire history was before us and we had decided to ignore certain of the former opinions and findings, we had no doubt that the condition was one of hemolytic ictero-anemia with life-long recurrences of jaundice, fever and anemia, with progressive splenomegaly, with extremely fragile erythrocytes

¹ *Loc. cit.*

progress was uneventful, the blood count rapidly rose to normal in red cells and hemoglobin; the white cells and platelets showed the usual postsplenectomy increase. Later Howell-Jolly bodies appeared in the red cells in the usual numbers. From the time when postoperative convalescence was terminated, the patient's health has steadily improved and for the first time in his life he has appeared entirely normal and healthy.

Discussion.—As one reviews this case report one cannot help but be impressed by the fact that the history as a whole is obviously that of hemolytic ictero-anemia. And yet certain individual items kept this patient for years from being correctly diagnosed and from being cured by splenectomy.

Much of the confusion centered about the jaundice. On at least one occasion the fact that there was evidence of an obstructive element in the jaundice misled the physicians. In the classical case there is yellowness of the skin but little of the sclerae, and no bilirubin in the urine. This explains the old name for the disease, acholuric jaundice. Meinertz considers an increase of bilirubin in the blood the basic symptom of this disease. This jaundice is, however, not a true obstructive jaundice and it is urobilinogen and urobilin which occur in the urine.

Obstructive jaundice may, however, occur, being superimposed upon the hemolytic picture and in fact resulting from it. When very active red cell destruction is taking place there may be such an excessive liberation of pigment that some damming back may occur in the liver. Also these patients have a high incidence of gallstones. Our case is a warning against allowing the diagnosis of obstructive jaundice, of cholecystitis or cholelithiasis to lead to the overlooking of the underlying hemolytic ictero-anemia. This mistake was made in the present case by an excellent gastro-enterologist who has written extensively on biliary subjects.

On another occasion too much reliance was placed on a test of the red cells' resistance to hemolysis by hypotonic sodium chloride solution. This was the result of several conceptions, first, that the symptom is of such constancy and importance that in its absence the diagnosis cannot be made and, secondly, that the test is so reliable that such a degree of con-

was jaundiced as a child and was operated upon for gallstones at the age of twenty-eight. A brother of the patient had jaundice following an attack of "grippe." Unfortunately no examination of this individual has been made but this history is certainly suggestive. Such history, however, is not essential to the diagnosis.

Summary.—Hemolytic ictero-anemia is characterized by a group of clear-cut symptoms all of which are usually present. There is good evidence, however, that in rare instances one or other of these classical symptoms may be absent. It is not proper to demand the presence of every symptom and the diagnosis should not be excluded upon the absence of one of these classical symptoms.

A case is reported in which the diagnosis of hemolytic ictero-anemia had been prevented on previous occasions by the lack of definite familial history, by the presence of obstructive jaundice, by the absence of increased erythrocyte fragility. When finally the correct diagnosis was made it was in spite of a distinctly aplastic red cell picture. The correctness of the diagnosis was proved by further study and the remarkable results of splenectomy.

and except at the height of the last attack, an active red cell forming bone marrow.

The results of splenectomy justified the diagnosis, and the boy's miraculously improved health since completes the evidence.

It may be noticed that we have not discussed the question of whether the boy's hemolytic ictero-anemia was of the familial congenital variety or of the acquired type. This distinction has in the past been given much emphasis. The familial variety is often spoken of as the Chauffard-Minkowski type, while the acquired is termed the Hayem-Widal type. Many attempts have been made to find differences in the symptoms and prognosis of the two forms, but with little success. Today it is generally accepted that all of the cases are congenital or familial and that the instances of so-called "acquired hemolytic ictero-anemia" are merely congenital cases which have for years been so latent as to escape recognition. If this is true, it would explain the long accepted view that the acquired form is always active or severe while the congenital form may either be active or so latent that the patient, as Chauffard said, may be "more icteric than sick." In other words, what was formerly termed the acquired type is composed always of previously latent cases in an active period.

It is not always possible to demonstrate the presence of the latent disease in members of the patient's family. Always they should be examined for splenomegaly, jaundice, and especially for lessened resistance of the red cells to hypotonic sodium chloride solution. The failure to find familial evidence of this disease tendency should not be given much weight in the diagnosis of the disease.

In our case one of the previous consultants stated in writing that the diagnosis of hemolytic jaundice, another name for hemolytic ictero-anemia, was "not tenable because of the absence of familial tendency and hemorrhages. The fragility is not sufficiently marked."

When one does investigate the family history, one does obtain, however, most suggestive items. The patient's mother

tion and the discolorization seemed to extend into the parenchyma of the tonsils. There were no palpable lymph nodes in the neck. The nasal chambers and paranasal sinuses were negative.

On account of his impaired general health, and the obscure lesion of the faucial tonsils, the patient was admitted to the Jefferson Hospital for a general survey and diagnosis, with the following results:

Physical Examination by Dr. H. K. Mohler.—"The patient is apparently a normal, moderately well-nourished individual, complaining of distress in the epigastrium after eating. There is no dyspnea, cyanosis or jaundice present.

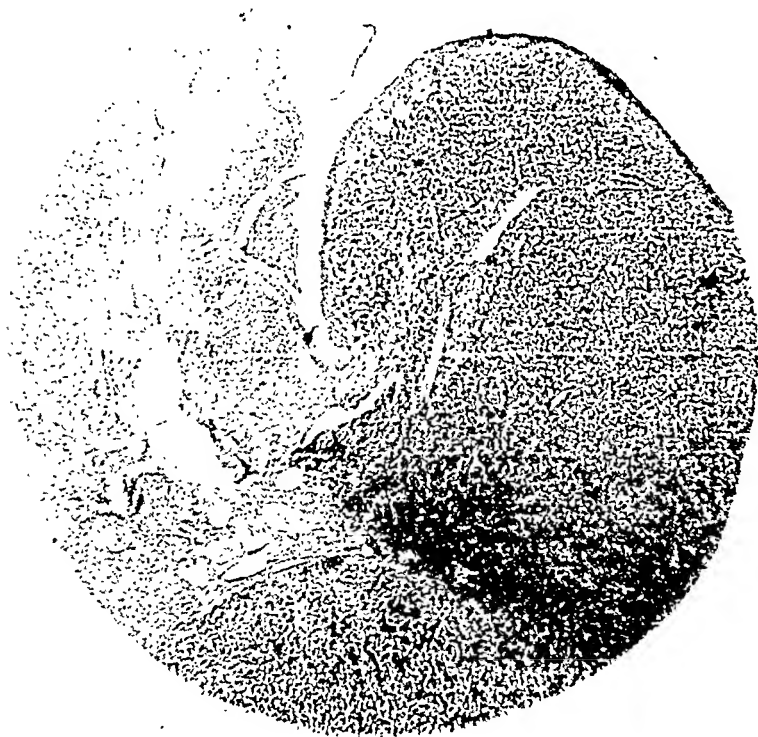


Fig. 102.—Microphotograph of section from growth involving tonsil. At the left, normal tonsil tissue is observed and the dark cellular area at the right is growth composed of deeply pigmented cells. ($\times 50$.)

"Neck: The thyroid gland is not enlarged, there are no enlarged lymph nodes or undue arterial pulsation or venous distention present. On the left of the neck, just below the hair line, there is a pigmented mole 1.25 cm. in diameter, almost covered with a faint, thin, hairy growth. There is no evidence of increased vascularity. No signs of inflammation in or about the mole are noted.

"Chest: The chest is symmetrical in outline. The expansion is equal. The lungs are clear and resonant throughout. In the lower half of the left chest

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MELANOMA OF THE FAUCIAL TONSILS, METASTATIC; CASE REPORT

I AM prompted to report this interesting case of melanoma because of the unusual symmetrical and bilateral involvement of the faucial tonsils, secondary to a small melanotic skin lesion on the neck, and to point out the risk incurred in the application of meddlesome therapy or inadequate surgery to apparent innocent lesions of the skin.

Case Report.—November, 1932, Mr. J. N., aged forty-two, a barber by occupation, was referred to me for an opinion as to his tonsillar condition.

Chief complaint was "indigestion," quite acute since July, 1932. Blood spitting during the last two months. Rough and uncomfortable feeling of the throat since October, 1932.

Family history was inconsequential.

Personal history revealed that his general health was quite good until recently, excepting an occasional gastro-intestinal disturbance of which he had complained for the past twenty years. An attack of acute tonsillitis some years previously. There have been no operations.

In the spring of 1932, he had electric treatments applied to a pigmented mole located on the left side of his neck. Several applications were administered. It is interesting to note that shortly after these treatments, most of his symptoms developed. Previous to July, 1932, he consumed large quantities of alcohol and used tobacco in excess.

Present illness.—In July, 1932, the gastro-intestinal symptoms became exaggerated. Abdominal pain was severe and continued except when lying down. Internal medication and diet failed to give any permanent relief. The patient stated that examination of his throat in October, 1932, revealed evidence of infection and a peculiar discolorization of both tonsils. Since that time, he has had daily blood spitting, has lost 28 pounds in weight and feels extremely weak. No sore throats, but is conscious of some discomfort.

At the time of my examination, the patient was fairly well nourished, anemic in appearance and somewhat apprehensive. The faucial tonsils presented a most unusual appearance. Involving the upper half of both faucial tonsils was a bluish-tinged tumor-like formation, resembling a hemangioma. There was no pulsa-

gen-ray study of the chest and gastro-intestinal tract; a complete blood study to determine the presence of a primary anemia."

Roentgen-ray examination made by Dr. W. F. Manges is as follows: "There are a large number of small fairly sharply defined tumor nodules scattered throughout both lungs, the miliary type of lung metastasis. The largest tumor is about the size of a pea; there are others smaller—from that to a very minute size."

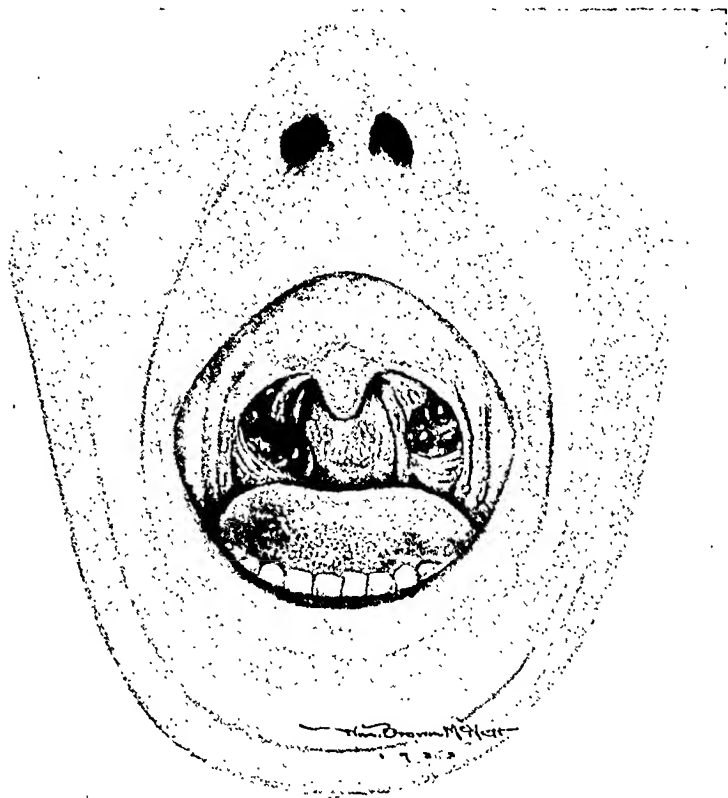


Fig. 104.—Drawing showing the tonsillar lesions.

Blood Count.—Hemoglobin, 73; red blood cells, 4,250,000; white blood cells, 9000; color index, 86; polymorphonuclears, 68 per cent; large polymorphonuclears, 3 per cent; large monocytes, 3 per cent; eosinophils, 3 per cent; basophils, 1 per cent; lymphocytes, 22 per cent. Coagulation time, five and one-half minutes. Bleeding time, two and one-half minutes. Wassermann and Kahn tests, both negative.

The right tonsil was removed and submitted to Dr. B. L. Crawford for pathologic study, the report of which is as follows: "Specimen consists of two

posteriorly and extending around anteriorly joining the heart fulness is an area of flatness and absence of breath sounds. The heart is normal in outline, the sounds are well heard and occur regularly. No shocks, thrills or murmurs are present.

"Abdomen: Distention is present. The liver is palpable, smooth in outline and extends 12 cm. below the costal margin in the right midclavicular line. The spleen is readily palpable and enlarged. The surface is smooth, extending 3 cm. below the costal margin in the left anterior axillary line. Ascites is not present.

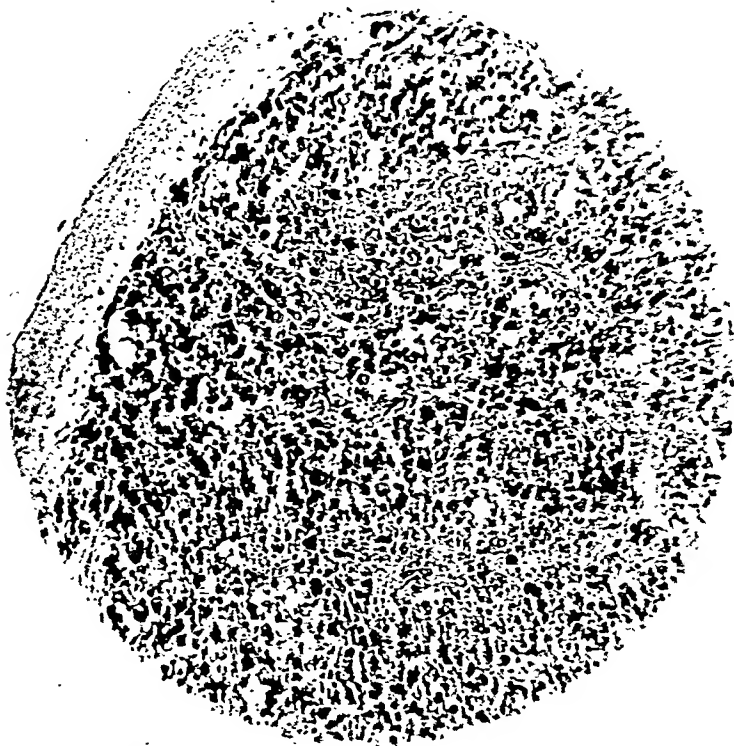


Fig. 103.—Microphotograph of higher magnification of growth revealing the large deeply pigmented melanotic cell. The mucosa of tonsil is observed at one margin. ($\times 150$.)

"Lymph nodes: No general adenopathy, except probably a few enlarged lymph nodes in both inguinal regions. The skin is warm, moist, of a normal texture and color. No other pigment moles are present.

"Extremities: There is no tremor present in the extended hands. The patellar reflexes are normal.

"Comment and suggestions: In view of the pigmented mole on the neck recurring twice after the use of electrical treatments and a history of indigestion, the following are suggested to aid in establishing the diagnosis: Roent-

by Stander.⁸ Although infrequent in proportion to the formerly widespread use of this anesthetic, such accidents have emphasized the dangers of chloroform aside from the possibility of its causing sudden heart failure. They are partly responsible for the gradual abandonment of the use of this drug since some of the cases have occurred after even the small amounts which are used in obstetrics. Except that ulcerating and necrotic lesions are not found in the upper gastro-intestinal tract when chloroform poisoning occurs after it is given by inhalation the pathology and symptomatology in these cases are very similar to those in which poisoning is produced by ingestion. The toxic action of chloroform is systemic in its effects and the local changes in the mouth and stomach are relatively unimportant.

Case Report.—The patient was a colored man of thirty-nine whose past medical history was negative except for luetic infection. He worked in an "animal refuge" and used chloroform to kill dogs and cats. For a number of years he had been a rather heavy drinker. On the night of February 16, 1933, while slightly intoxicated and very despondent he decided to commit suicide and drank chloroform. Almost immediately after taking the chloroform the patient became unconscious. He was rushed to the hospital at once and reached the accident ward within fifteen minutes after swallowing the drug. At that time the patient was in deep coma and could not be roused. There was a distinct chloroform odor to his breath. All of the reflexes were absent. The pupils were somewhat contracted and were fixed. The heart and lungs were normal, the pulse 70 and of fair volume and the temperature 95 F. Stimulants were administered and the stomach lavaged. A large amount of food material strongly smelling of the drug was obtained. Probably because the coma was so deep as to abolish the cough reflex some of the lavage fluid was inspired. The coma persisted for twelve hours.

The following morning the patient was conscious and rational. He told of his desire to commit suicide and stated that he had taken 6 ounces of chloroform. He complained of burning in his mouth, the mucous membrane of which was quite red, and substernal and epigastric soreness. These symptoms were increased by taking food. There was vomiting of blood-streaked material. The sclerae were slightly icteric and there was tenderness over the liver, which was slightly enlarged.

Later the same day the patient became irrational. The following morning jaundice was much more marked. Vomiting persisted. The liver was enlarged to three fingerbreadths below the costal margin. At this time it was also noted that suppression of urine was beginning. After a slight improvement in the mental condition the irrationality became more marked. Jaundice gradually deepened and subconjunctival hemorrhages developed. On February 23rd, one week after admission, ascites was noted. The patient sank into coma.

small, irregularly shaped masses of tissue. One measures $1\frac{1}{2} \times 1\frac{1}{2} \times 1$ cm. The base of the tissue is soft and gray. Projecting from the surface is a dark brownish-black nodule which measures $1\frac{1}{2}$ cm. in its greatest dimension. The line of demarcation between the black nodule and the underlying gray tissue seems to be sharply defined. There is a small cyst in the gray tissue. The other nodule is composed of a similar structure. On one surface is a much smaller projecting nodule.

"Histology.—Examination of sections from the tonsil reveals that the above described nodule which protrudes above the surface is composed of masses of large irregularly shaped cells, which contain a large amount of dark brown pigment. The cells vary considerably as to size and shape, and in some areas the tumor cells contain much more pigment than in other areas. The growth seems to be rather vascular. The nodule seems to be confined within the tonsil membrane as it is partially covered by mucous membrane but is inflamed and ulcerated in one surface. The smaller nodule is composed of tumor cells of a similar character.

"Diagnosis.—Melanoma, malignant, of the tonsils."

Summary.—Stimulating or irritating electric applications to a pigmented mole on the neck evidently produced a rapid malignant change with almost immediate widespread dissemination to the lungs, liver, tonsils and perhaps other organs, which could have only been determined by postmortem examination. As the patient died at home two months after the diagnosis was made, a postmortem was not obtained.

It occurs to the writer that one inexperienced in the pathology, clinical course, and treatment of pigmented moles of the skin, should keep hands off until advice is sought from a surgeon experienced in the treatment of malignant tumors. Wide and thorough excision is the treatment of choice.

Despite the giving of fluids by nasal tube and by vein there was practically no output of urine. The jaundice continued to be quite deep. Respirations were labored and the abdomen distended. On the next day the coma was deeper. All reflexes, including cough and swallowing, were absent. Signs of pneumonia were noted and the temperature rose. The patient died on February 25th, nine days after taking the chloroform.

At the time of admission the urine was negative except for a trace of albumin and the blood count was normal. The Wassermann reaction was strongly positive. The following table summarizes the other laboratory findings.

Treatment after the initial stimulation and lavage consisted of sedatives (morphine was avoided because of the evident liver damage), intravenous glucose solution and small doses of insulin. Large amounts of fluid were given by nasal tube and bicarbonate of soda was added to this.

Autopsy Findings.—The autopsy was performed three hours after death. The body was that of a well-developed mulatto and was moderately jaundiced. The sclerae were bile stained and showed many petechial hemorrhages. There were also petechiae of the gums. The abdomen was distended and when the peritoneum was opened 1700 cc. of bile-stained fluid was removed. No fluid was found in the pleural or pericardial sacs.

The heart was normal in size. The valve leaflets were essentially normal but the aorta showed slight atheromatous changes. On microscopical examination the heart muscle showed nothing significant.

Both lungs were very congested and contained small scattered patches of pneumonic consolidation.

The spleen weighed 130 Gm. It was congested and the pulp was soft. The connective tissue was somewhat hyperplastic. There were thickening and hyaline degeneration of the arterial walls.

The stomach was distended with dark fluid. Congestion was marked especially near the cardia and along the greater curvature and in these locations there was some patchy necrosis of the mucosa. There was also congestion of the duodenum. The colonic mucosa was somewhat edematous and at the rectosigmoid junction many petechial hemorrhages were seen.

The liver weighed 1540 Gm. It was heavily bile stained and firm. The capsule showed no changes. Areas of congestion and fatty infiltration were seen on the cut surface. Microscopical study showed extensive necrosis of the liver lobules. This was mostly central in location but in a few areas the necrosis seemed to begin in other portions of the lobule. The necrosis was so extensive that as much as one half of many of the lobules was destroyed. The central veins were distended. Scattered through the necrotic areas were a few red blood cells and also leukocytes and lymphocytes. There was also much fat, as was demonstrated by the sudan III stain. In the nonnecrotic areas of the liver the cells were fairly well preserved. The nuclei were not degenerated. The cell columns were separated by distended capillaries. There was no evidence of regeneration of the liver tissue and no proliferation of the fibrous tissue. The epithelium lining of the bile ducts was intact but the nuclei here showed some degenerative changes.

The kidneys were somewhat enlarged, weighing 240 and 280 Gm. They were soft and the cut surfaces moist and congested. The cortex and medulla were well

	Blood sugar.	Blood urea N.	Creatinine.	CO ₂ combin- ing power.	Cholesterol.	Serum bilirubin.	Urobil- inogen.	Leucine and tryo- sine.	Albumin Globulin.	Coagulation time.	Dye retention.
2/17/33	147	25	1 : 50				
2/18/33	150	40	3.4	34	...	5	1 : 30	0	2.84 — 1.42		
2/20/33	96	70	10	202	20	0				
2/21/33	...	85	12.4	204	30	2½ mins.	
2/22/33	...	110	13.6	30	4.56 — 1.10	90%
2/23/33	...	120	14.1	15	...	20					
2/24/33	110	138	16.1	14	216	20					

Galactose tolerance tests were attempted on two occasions but because of the suppression of urine it was impossible to obtain satisfactory specimens.

Hirsch stressed the hepatic damage. This is the more surprising since so much of the recent work has been directed almost exclusively to the effect of this drug on the liver. This has led to the belief that liver damage is the chief cause of death. It is possible that the pathologic changes in this organ have been somewhat overemphasized and that the opinion of Williamson and Mann¹¹ that, though the liver is the most seriously damaged organ, chloroform is a general protoplasmic poison and effects the entire body, is more nearly correct.

Pathologic Changes.—The necropsy findings depend to a certain extent on the speed with which death occurs. In Schoenhof's case, for instance, death occurred in a few hours and aside from the local necrotic changes in the esophagus and stomach nothing of importance was found. In most cases, however, and also in experimental animals, there are significant pathologic changes, particularly in the liver and, to a lesser degree, in the kidneys. The heart and spleen are also frequently damaged but usually not to an important extent.

The speed with which liver damage is produced has been recently stressed by Anderson,¹² who found mitochondrial changes within a few minutes after the onset of chloroform anesthesia. Kochmann¹³ also mentions the rapidity with which cell destruction may occur. As noted by M'Gowan,¹⁴ the essential changes in the liver go through the sequence of cloudy swelling, fatty degeneration, removal of the fat and shrinking and disappearance of a cell. This process may be passed through within a short time so that even within twenty-four hours after the poison has acted the picture may resemble a primary necrosis. The degenerative and necrotic changes may begin peripherally, centrally or in the intermediate portion of the lobule.¹⁵ Usually, however, the necrosis begins in the center of the lobule and extends rapidly toward the periphery, frequently involving much more than one half the lobule. The bile ducts are not damaged. Lime salts are frequently deposited in and around the necrotic areas.¹⁶ Fat is more apt to be found in the border surrounding the necrosis than in the destroyed cells. Glycogen is usually absent from the extremely

differentiated. The capsules stripped readily. Histologic examination showed the capillaries of the glomerular tufts to be congested and the tuft capsules contained some albuminous material. The epithelial lining of the convoluted tubules showed cloudy swelling and hyaline and fatty degeneration and the tubules contained casts formed of cell debris and hyaline material. The epithelium of the collecting tubules was normal and no change was seen in the interstitial tissue or blood vessels.

Symptoms.—The symptoms produced by the ingestion of chloroform are very similar in most of the reported cases. If the amount of the drug taken is small or if the stomach contains much food there may be a short period of excitation before the patient becomes unconscious. Ordinarily, however, this is absent and unconsciousness occurs almost immediately. This is usually very deep so that all the reflexes are abolished. The abolition of the vomiting reflex may be an added factor in increasing the severity of the effects of the poison. The pupils vary in size. The pulse and respiration are quite shallow and chloroform odor is on the breath. In approximately one half the fatal cases death occurs in the initial coma.¹ If the patient survives this coma, consciousness is regained in a few hours and there may be no complaint save substernal and epigastric soreness from irritation of the esophagus and stomach. If this irritation is marked there may be bloody vomiting and diarrhea. At this time the patient may seem perfectly normal mentally but in those cases which go on to a fatal outcome irrationality and delirium soon appear and after a few days more these gradually give way to the coma which precedes death. Jaundice is mentioned with varying frequency in the reported cases. Ernberg says that it occurs irregularly and Hirsch⁹ mentions it in the summary of only one case. Schelcher, on the other hand, feels that jaundice is usually present. Hemorrhages from the stomach and bowel occur in most cases. It is important to note that these are not entirely due to the local action of the drug since they are also seen when the poisoning follows chloroform anesthesia.¹⁰

Opinions vary as to the actual cause of death. Ernberg felt that pneumonia and gastritis were most important but also considered kidney damage as a possible factor. Neither he nor

unable to support the view that hydrochloric acid is the toxic factor in chloroform poisoning. They were also unable to prevent the occurrence of liver lesions by the feeding of foods having alkaline ash. Davis and Whipple²⁴ also noted no protective effect from sodium bicarbonate. Wells¹⁸ states that the fatty changes produced by the drug may be due to the suppression of the oxidizing enzymes. This leaves autolytic enzymes and lipase free to digest the liver cells and form fat. This theory, however, is lacking in experimental proof.

The easy solubility of chloroform in fats has been emphasized in discussing the predilection for the drug to attack the liver. M'Gowan¹⁴ has stated that the cells are liable to damage in proportion to the amount of fat which they contain. Opie and Alford²⁵ and Davis and Whipple²⁴ noted that feeding of fats to animals markedly increases their susceptibility to poisoning. The former workers mention that fat feeding causes infiltration of fat particularly in the center of the liver lobules and in the loops of Henle and that the necrosis caused by chloroform has the same location.

The previous state of nutrition of the experimental animal has been shown to have some bearing on the ease with which the drug causes liver damage.^{24, 25} The glycogen content of the liver cells has been considered to be an important protective factor.²⁶ Reducing this by starvation or by thyroid feeding markedly increases the susceptibility of the liver to damage, while the administration of carbohydrates is a valuable prophylactic measure. This has been stressed in cases of delayed chloroform poisoning by Royston,²⁷ whose patients had had long and difficult labors and had been without food for several days. As an additional predisposing factor Royston mentions infection with resulting liver damage. This point is emphasized by others who have observed that delayed chloroform poisoning is more apt to occur in patients who are operated upon for some purulent focus in the abdomen. Wells²⁸ is of the opinion that previous liver disease is important in increasing susceptibility to the drug and Brunner²⁹ states that only a diseased liver can be damaged by chloroform anesthesia. The

damaged livers.¹⁷ Wells¹⁸ has demonstrated that, just as in acute yellow atrophy, the liver of chloroform poisoning contains an abundance of free amino-acids.

Although Fiessinger¹⁹ claimed to be able to produce cirrhotic changes by means of chloroform, Whipple and Sperry²⁰ and de Zalka¹⁷ have emphasized the speed and completeness of liver regeneration after damage by this drug. The necrotic cells are removed by the phagocytic action of endothelial cells. De Zalka states that in rabbits most of the necrotic cells have disappeared in four and one-half days. Repair is affected by rapid multiplication of the remaining healthy cells and, at least in dogs, the liver becomes essentially normal again in two or three weeks.

The pathologic changes in the kidneys have received much less experimental attention than those in the liver. Terschen-dorf²¹ was able to produce degenerative changes in the tubular epithelium with the drug. Most of our knowledge of the changes in the kidneys is dependent on the autopsy findings in a few cases. Kochmann states that renal disturbance may be absent even when severe hepatic damage has been produced. The cases of both Ernberg and Schelcher showed cloudy swelling and fatty degeneration of the tubular epithelium as did a number of those who died after chloroform anesthesia. It is important to remark that the glomeruli are never involved in these changes but that the damage is always confined to the tubules and largely to the convoluted tubules.

Pathogenesis.—The manner in which chloroform produces its harmful effect on the liver has been variously explained. Graham²² concluded that the toxic action is not peculiar to chloroform but is a group reaction characteristic of the alkyl halides and is due to the liberation in the body of free acids, in this case hydrochloric acid. He felt that by the administration of hydrochloric acid all of the features of chloroform poisoning could be reproduced except localization of the lesions in the center of the lobule. Graham also stated that sodium carbonate would inhibit the experimental production of liver damage. Underhill and Kapsinow²³ reviewed Graham's work and were

injuries. With recovery of the liver the fibrinogen rapidly returns to normal.

The reduction in fibrinogen is looked upon by Whipple and Hurwitz as being a good index of the amount of liver dysfunction which the chloroform causes. In addition to this Whipple and Smith³¹ and Smyth and Whipple³² have reported that even very small amounts of the drug cause a marked decrease in the amount of bile acids produced by the liver cells. Marshall and Rowntree³³ studied the liver and kidney function in experimental chloroform poisoning in dogs and were able to show that the drug causes decreased dye excretion by the liver, an increase in blood lipase, a lowering of blood fibrinogen and a decrease in the tolerance toward galactose and levulose. Whipple and Speed³⁴ also reported a decrease in phenoltetrachlorophthalein excretion after chloroform was given to animals. The only clinical studies are those of Widal, Abrami and Hutinel³⁵ who demonstrated that liver dysfunction, as measured by the hemoclastic crisis, was more marked after chloroform than after other anesthetics.

In this patient the chief evidence of liver disturbance was the jaundice itself. The bromsulphalein excretion was tested on one occasion and 90 per cent dye retention was found. The urobilinogen test on two occasions before the jaundice became very marked gave slightly positive results. Unfortunately, the galactose test could not be satisfactorily performed because of the anuria. This test is positive in a very high percentage of cases with acute icterus of hepatocellular origin.³⁶ This case would have served as a valuable check on the accuracy of the test. Although fibrinogen was not determined, the coagulation time at the height of the illness was normal.

The anuria which developed probably had a multiple explanation. The decrease in urinary output was first noted on the second day after admission and at this time seemed due to the inability to retain fluids. Later ample fluids were given by vein but despite this the suppression of urine increased. At the time ascites was first noted, one week after the drug had been taken, anuria was complete. The relative importance of

frequency of deaths from chloroform anesthesia in children and healthy young adults, however, makes universal application of this thought seem somewhat incorrect.

It is difficult to determine the importance of these antecedent factors in the patients who have been poisoned by chloroform ingestion since in most of the reported cases the state of nutrition or the existence of infection is not noted. Undoubtedly the presence of large amounts of food in the stomach would have some protective action both locally and by delaying absorption of the drug. The patient reported in this paper was a chronic alcoholic. This may have caused increased susceptibility by inducing fatty changes in the liver. It seems unlikely, however, that even a completely healthy individual could have withstood the effects of the amount of chloroform which he took.

It is interesting to investigate the mechanism which produced some of the symptoms and laboratory findings which this patient showed. In his case jaundice was a prominent symptom. In earlier papers, such as that of Schelcher, this was ascribed to hemolysis and also to duodenal catarrh with resulting biliary obstruction. No evidence has ever been produced to prove that chloroform has any hemolytic activity and, although there is undoubtedly a great deal of mucous membrane edema and destruction it is much more probable that the jaundice is caused by the intense damage to the liver cells themselves.

The hemorrhages in this patient were not limited to the mucous membrane of the upper gastro-intestinal tract but were also found in the subconjunctival tissue and in the colon. They are, therefore, not entirely due to local destructive action of the drug. As a matter of fact, hemorrhages into the bowel have been seen in cases in which chloroform poisoning followed its use as an anesthetic.¹⁰ It has been shown by Whipple and Hurwitz³⁰ that the administration of this substance will cause a marked drop in the fibrinogen of the blood. The decrease in fibrinogen is in proportion to the degree of liver necrosis. In severe cases fibrinogen may be almost entirely eliminated from the blood and the animal may bleed for hours from very slight

noted in animals by Bodansky.⁴⁰ Guided by the severity of the liver damage, Williamson and Mann¹¹ expected that hypoglycemia would be frequently found in experimental chloroform poisoning. As a matter of fact they found it only occasionally and then as a terminal event.

The blood cholesterol is frequently low in severe liver cell disease. It was slightly elevated in this patient. Gray⁴¹ has reported an increase in cholesterol in rabbits following the administration of chloroform. No explanation is known for this other than that it probably represents some disturbance in lipid metabolism, possibly an inability of the liver to excrete this substance.

The increase in urea nitrogen and creatinine was probably due to the combined effects of a marked increase in protein catabolism and retention from kidney insufficiency. The chemical changes following poisoning with this drug have been particularly studied by Stander.⁸ He noted a disturbance in the nitrogen partition in the urine, the urea nitrogen being diminished. The blood in his cases showed a marked increase in all of the nonprotein nitrogen elements with a marked rise in the amino-acids. The last change was ascribed to loss of the deaminizing activity of the liver. Acidosis also occurred in Stander's patients and was found experimentally by Marshall and Rowntree.³³

Prognosis.—In the two reported series of cases poisoned by the ingestion of chloroform, those of Hirsch and Enrberg, the mortality is slightly less than 50 per cent. In individual cases it is difficult to accurately determine the prognosis. The outcome is probably influenced by such factors as the amount of food in the stomach at the time the drug is taken, the promptness with which the vomiting reflex is abolished and the presence of previous liver disease which might render that organ more susceptible. The fatal dose is quite variable. Peterson, Haines and Webster⁴² state that death occurred after 15 Gm. and recoveries after 70 and 222 Gm. In most of the fatal cases which they collected from the literature the dose was between $\frac{1}{2}$ and 2 ounces. In Hirsch's series there was no striking differ-

either the liver or kidney damage in producing this symptom is difficult to state. The relation of the liver to water metabolism is now well established and in marked liver disturbances, such as acute yellow atrophy, diminution in the amount of urine usually occurs. It seems more probable, however, that the anuria was largely produced by the renal damage. This patient had degenerative changes in the epithelium of the convoluted tubules. The glomeruli were essentially normal. The kidney changes were similar in distribution to those seen in bichloride poisoning, which is also characterized by anuria. Richards³⁷ studied the functioning of the frog's kidney when subjected to bichloride. He found that, despite the anuria, the glomeruli separated fluid from the blood at a rate even greater than normal. Because, however, of the damage to the tubular epithelium, the osmotic pressure of the serum proteins was able to draw practically all of the glomerular filtrate back into the blood so that practically no urine left the ureter. It is probable that this explanation can also be applied to the anuria in this patient. Whether the kidney damage was due to the effect of the chloroform or whether the kidney lesions resulted from some toxic substance liberated by the necrotic liver is impossible to state. Helwig and Orr³⁸ have reported a case of traumatic necrosis of the liver with marked nephrosis and creatinine retention.

The ascites was another symptom for which no simple explanation could be offered with certainty. It has been reported in some cases of acute yellow atrophy³⁹ and seems to result from a disturbance in the portal circulation which is much too acute to permit establishment of collateral channels. Another possible cause is toxic damage to the peritoneum. It seems unlikely that the ascites resulted from the renal changes since there was no fluid in the other serous sacs and no edema. At the time the ascites developed the serum proteins were normal.

The changes in this patient's blood chemistry were also interesting. At the onset he had slight hyperglycemia. This is comparable to the initial hyperglycemic effect from chloroform

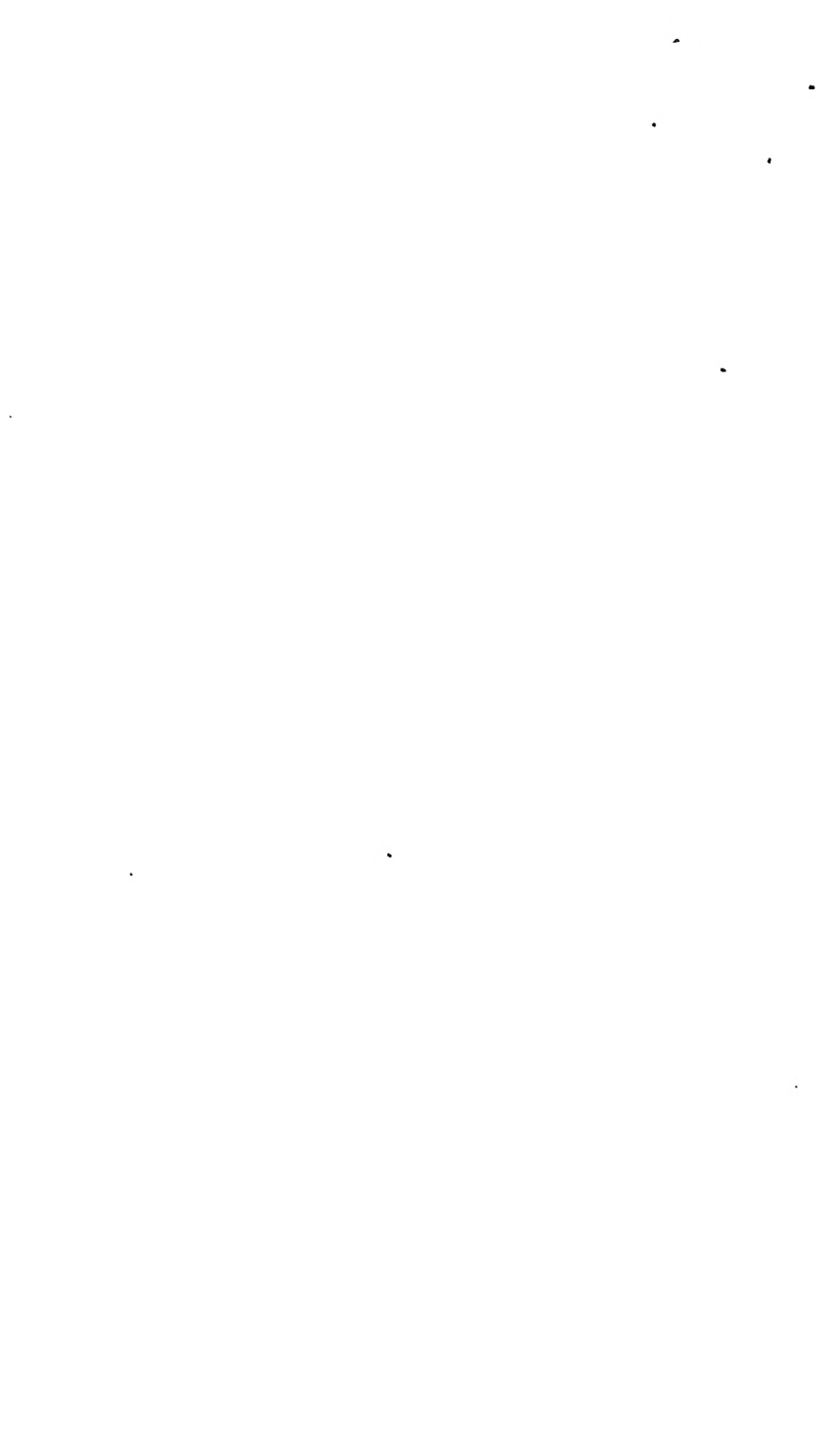
licated to prevent toxic action of the hydrochloric acid liberated from the chloroform. Although this has not been substantiated the marked acidosis may be relieved by alkaline therapy. It is important to recall that in cases such as this one, in which there is such extensive hepatic damage, morphine is contra-indicated, since the detoxifying action of the liver is lost. If, therefore, sedatives are needed, one of the barbiturates is to be preferred.

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ence in the amounts taken by those who died and those who recovered. As has been noted the occurrence of an apparently normal period after the initial coma is not necessarily a favorable indication. The patient may again lapse into unconsciousness and die. From the work on animals it may be concluded that if the patient survives the period of acute poisoning the restoration of health and satisfactory hepatic function should be fairly complete. Whipple and Sperry's²⁰ dogs had normal livers in two or three weeks after the experiments were finished.

Treatment.—There is no specific antidote for chloroform. Wirth² recommended that the initial gastric lavages be done with warm oil instead of water because of the solubility of the drug in the former substance. He had one recovery after such treatment and it is interesting to note that in 2 cases who recovered, those of Hirsch and Wollenweber,⁴³ the chloroform was taken mixed with oil. After the gastric lavages have been done the only treatment which is of any value is the administration of glucose. If the patient can swallow, it may be given by mouth, otherwise it should be given by tube or by vein in the form of slightly hypertonic solution. Since the purpose of this treatment is to stimulate the deposition of glycogen in the liver it should not be given at a rate which exceeds the speed with which the body can assimilate it. As Woodyat, Wilder and Sansum⁴⁴ have shown this is approximately 0.85 Gm. per kilo of body weight per hour. There is ample evidence that the liver cell can function satisfactorily only when it contains adequate glycogen so that this form of treatment is certainly indicated by the extensive liver damage. It is questionable whether insulin should be given with the glucose. Many workers, such as Lauda,⁴⁵ feel that it aids greatly in helping the liver store glycogen, while Althausen⁴⁶ concluded that more glycogen is stored by the liver when insulin is not used. There seems, however, to be no contraindication to the use of small doses of insulin, although they may be of no benefit. In addition to glucose, sodium bicarbonate may be given by nasal tube. Graham felt that the administration of alkalis was in-



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of these cases showing a typical picture of pernicious anemia following destructive changes in the stomach. The anemia of *Bothriocephalus latus* infestation is similar in its appearance and may be possible of explanation by toxic changes in the mucosa. Pathologic reports on the gastric mucosa post-mortem are infrequent and unsatisfactory as most changes found are attributed to postmortem digestion. There is, however, no doubt that the clinical picture of so-called "primary pernicious anemia" may be produced by gastric destructive processes and there is no doubt that prompt amelioration of the condition can be secured by administration of adequate amounts of liver extract, gastric substance or, as Castle has shown, by beef digested by normal gastric juice.

The criteria for the diagnosis of pernicious anemia have been augmented by the reports of recent workers already referred to. As Spiller emphasized years ago, the nervous and cord symptoms may indicate this disease, in some cases, for years before any anemia is apparent. The achlorhydria is suggestive but may be present with anemia of a different type. The atrophic tongue is suggestive, but not pathognomonic. The picture of a progressive anemia with remissions, without wasting, with achlorhydria, atrophic tongue, cord symptoms and response to specific therapy serves to classify a patient as belonging to this group which we have termed primary pernicious anemia and which we now find may in some cases be shown to be secondary to demonstrable gastric damage. It would seem that complete achylia is not essential to the diagnosis.

As will be shown we may find patients in whom anemia is not apparent who show marked nervous symptoms and who benefit to a striking degree by specific therapy. This symptom complex is seen or is recognized frequently among our white hospital patients but seldom among the colored.

Case I.—H. S., aged forty-eight, white. Admitted January 1, 1933. Discharged February 14, 1933.

For two years prior to admission patient suffered with abdominal fulness after meals and occasionally was nauseated and vomited after meals. This was usually preceded by "pains in the stomach." Had been slightly jaundiced at

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ANEMIA DUE TO GASTRITIS OCCASIONED BY ALCOHOLISM; CONSIDERATION OF CASES OF PURPURA, INCLUDING AN EXAMPLE OF PURPURA APPARENTLY SECONDARY TO PERNICIOUS ANEMIA

YOUR class has had an opportunity to observe a number of interesting cases of abnormal conditions of the blood in this year's session. The different cellular components of the blood may appear in decreased number due to increase in destructive factors, or to lessening in productive activity. Where increased destruction of cells by hemolysis can be demonstrated as the cause of their paucity the condition is termed "hemolytic anemia." Where formation of new cells is lacking and anemia results we term it "aplastic anemia." If no demonstrable cause exists it is commonly termed *primary* or *idiopathic*, while either increased blood destruction or decreased blood formation resulting from some independent demonstrable cause may produce *secondary anemia*. In considering the anemias where red cell lack exists you have seen cases of secondary extreme anemia due to repeated blood loss.

We shall consider today some cases of anemia showing the characteristic features of Addison's or pernicious anemia or the so-called "idiopathic anemia" which according to recent researches is possibly not primary, in that certain factors leading up to its production can be demonstrated. The studies of Whipple, Minot, Murphy, Castle and others have clearly demonstrated that damage of the gastric mucosa or lack of function in its cells results in a deficiency of some factor essential to red cell formation and maturation.

This has been shown in cases of gastrectomy and is well recognized in infiltrating carcinoma of the stomach wall, many

Case II.—R., a man of forty-five, had been a hard and steady drinker of whisky for many years. I saw him on account of acute alcoholism and apparent gastritis.

The gastric contents were aspirated with difficulty by lavage and showed great quantities of viscid mucus, no free HCl was present. The liver was enlarged and firm. He developed weakness in the legs and unsteadiness in walking, and knee jerks were lacking. Muscle sense was disturbed and vibratory sense lacking.

There were various vicissitudes in his physical condition over three or four years during which time he drank constantly and consistently. There was a variable hypertension, the pressure being noted at from 160 to 210 systolic, and an increasing firmness of the liver, increasing atrophy of the tongue, increasing ataxia and muscle weakness in the legs and increasing intolerance to food so that vomiting was frequent and little food retained for days at a time. There was a sudden acceleration in anemia which progressed very rapidly during the last two months of his life. At the time of death hemoglobin was 10 per cent or less by the Talquist scale and the red cells extremely irregular in size and shape with many macrocytes. Blood urea nitrogen was normal throughout. An attempt was made to administer HCl and the recently prepared liver extract but medication was refused or not tolerated and death ensued. Autopsy was not permitted.

There was no demonstrable infection and no loss of blood to account for this extremely rapid development of anemia which in all respects resembled pernicious anemia.

A second case may be cited similar to this in many respects.

Case III.—A., a woman, aged forty-six at death, had used alcohol and whisky to excess for many years. She had previously shown achlorhydria and for two years had wasting and weakness in the legs with disturbed reflexes and muscle sense. Walking was difficult and finally became impossible. There was a multiple peripheral neuritis. Bladder and bowel disturbance due to lack of control, and other signs of cord disturbance made their appearance.

She had suffered some attacks of tetany during two or three years. In the latter part of her illness a very rapidly progressive anemia became apparent, the red cell count dropping to 800,000 with great irregularity in the shape and size of the red blood cells. At this time vomiting was frequent and on this account, for days, practically no food could be taken.

Hydrochloric acid and liver extract were given and for a week improvement seemed definite, the blood count rose to 1,100,000 during this week, vomiting stopped and a fair amount of food was taken. There was definitely less weakness. The patient suffered an acute respiratory failure and died. There was no autopsy.

Another case seems to bear on this subject.

Case IV.—H., a man of fifty-five now under treatment.

He has been a steady drinker of whisky for thirty years. He drinks before breakfast and after dinner, as well as during the rest of the day.

times. Had had vertigo and weakness, at which time he noticed that he was more jaundiced. No hematemesis. Bowels were regular. During this period there was a tendency to drowsiness, which had increased, a tremor and weakness of the arms and legs, more noticeable in the morning. Unsteadiness in walking. Had been a heavy drinker of alcohol, whisky, and beer for twenty-five years.

There is nothing significant in the past medical history. Significant findings on physical examination show a well-nourished man appearing somewhat older than stated age, drowsy and apathetic but rational when aroused. There is a slight icteroid tinge to the skin. He complains of weakness and of abdominal discomfort and indigestion. The tongue is atrophic and smooth. The heart shows some enlargement to the left. Blood pressure, 120/80. Temperature, pulse and respiration normal.

The abdomen is tense and full. The liver enlarged and firm with well-defined sharp edge at the level of the umbilicus. The surface of the liver is finely nodular but regular in outline. Spleen not definitely felt, possibly due to voluntary rigidity of the abdominal wall. No ascites is demonstrable.

There is an absence of both the knee jerks and Achilles reflexes on either side and a positive Romberg test. Reflexes diminished in the upper extremities. Sense of position in the toes is faulty.

Laboratory studies showed red blood cells 2,810,000, leukocyte and differential counts were normal. Blood and spinal serological studies negative. Gastric contents showed an absence of free HCl in all fractions with a low total acid. Blood sugar was normal but the blood urea nitrogen on admission was 95, gradually falling to 21, where it remained stationary. Icterus index 33. Van den Bergh diphasic.

The patient, showing apathy, drowsiness and weakness with hepatic cirrhosis, gastric symptoms, and apparent renal insufficiency, will be given HCl before meals, liver extract intramuscularly, with added vitamins.

Here is a patient with atrophic cirrhosis probably due to alcohol. Gastric symptoms have been present for a long time. Chronic passive congestion of the stomach and bowel due to portal blockage in the liver give digestive tract symptoms, and in this case these symptoms might reasonably be attributed to this cause. We note, however, the atrophic tongue, the evident anemia, the complaint of awkwardness or uncertainty in walking and the tremor and unsteadiness in the hands and the lack of free HCl in the gastric contents and in comparing this patient with other individuals presenting a picture somewhat similar it seems worth while to consider the possibility that the anemia factor is important.

Let me cite very briefly three other cases bearing on this point:

Case II.—R., a man of forty-five, had been a hard and steady drinker of whisky for many years. I saw him on account of acute alcoholism and apparent gastritis.

The gastric contents were aspirated with difficulty by lavage and showed great quantities of viscid mucus, no free HCl was present. The liver was enlarged and firm. He developed weakness in the legs and unsteadiness in walking, and knee jerks were lacking. Muscle sense was disturbed and vibratory sense lacking.

There were various vicissitudes in his physical condition over three or four years during which time he drank constantly and consistently. There was a variable hypertension, the pressure being noted at from 160 to 210 systolic, and an increasing firmness of the liver, increasing atrophy of the tongue, increasing ataxia and muscle weakness in the legs and increasing intolerance to food so that vomiting was frequent and little food retained for days at a time. There was a sudden acceleration in anemia which progressed very rapidly during the last two months of his life. At the time of death hemoglobin was 10 per cent or less by the Talquist scale and the red cells extremely irregular in size and shape with many macrocytes. Blood urea nitrogen was normal throughout. An attempt was made to administer HCl and the recently prepared liver extract but medication was refused or not tolerated and death ensued. Autopsy was not permitted.

There was no demonstrable infection and no loss of blood to account for this extremely rapid development of anemia which in all respects resembled pernicious anemia.

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Case IV.—H., a man of fifty-five now under treatment.

He has been a steady drinker of whisky for thirty years. He drinks before breakfast and after dinner, as well as during the rest of the day.

He was examined by me several years ago, at which time he showed cirrhosis of the liver, hypertension and cardiovascular disease. Hemoglobin, 95 per cent. Blood urea nitrogen, normal. He recently presented himself for examination, complaining of difficulty in walking, awkwardness in use of legs and marked weakness of the legs, and feet, particularly the left, vomiting with large quantities of mucus, gagging, nervousness and insomnia. A tremor of the hand made writing difficult or impossible. There had been slight difficulty in writing for some years following an old neuritis in the right arm. There was no anemia, his hemoglobin showing 95 per cent Talquist, but the gastric symptoms and weakness of the legs, difficulty in walking and nervous symptoms were so similar to the findings in the two cases previously cited that he was instructed to take HCl before meals, vitamins in the form of haliver oil, and was given an injection of liver extract. Seen a few days later he reported that he was much stronger, was eating well, free from nausea and vomiting, gaining in strength and sleeping satisfactorily. He was much less nervous and walked much better.

His improvement has continued so that coincident with a few months' treatment, during which time gain has been steady, he has increased 15 pounds in weight, can walk for an hour at a time without fatigue, has an excellent appetite and sleeps soundly.

Cases II and III showed atrophic cirrhosis of the liver and chronic gastritis, cord symptoms and peripheral neuritis, atrophic tongue and history of achlorhydria in one case and lack of acid on one examination in the other. They terminated in an extremely rapid and extreme anemia having the appearance of pernicious anemia. In the first case liver extract in form for intramuscular administration was not available and medication by mouth was not tolerated. In the second case temporary improvement was apparent under the medication. This seemed sufficiently suggestive to warrant its trial in Case IV.

We know that pernicious anemia may result from gastric damage and that the gastric and nervous symptoms of pernicious anemia may exist for a long time without anemia being apparent. In Case IV, the result of the treatment, which is still being carried on, seems strikingly successful. There is sufficient similarity in the condition of the patient here presented (Case I) to the findings in these cases cited to warrant a trial of specific therapy as an experiment. It seems not improbable that gastric and liver damage of long standing, and due to alcohol, are concerned in the anemia and in the nervous symptoms which are evident, and with the combination of anemia,

achlorhydria, atrophic tongue and nervous symptoms, with signs of cord changes, specific therapy should be tried.

NOTE: Case I, after three weeks of treatment with liver extract, intramuscularly, dilute HCl and vitamins, was noted as having made rapid symptomatic improvement, was helping the orderlies in the ward, was alert and cheerful and felt strong, was eating and sleeping well and was discharged to the outpatient service for observation and further liver therapy.

The question arises as to what part was played by therapy in the cases treated, and how much the improvement was due to feeding, care and abstinence from liquor. It will be observed that the therapy used was adopted in a way as a therapeutic test to add information on the question of the probability of there being a condition similar to pernicious anemia, brought about by gastric damage. The results of treatment appeared to be favorable in both instances with a promptness and to a degree which did not seem a matter of coincidence.

Before treatment was instituted in Case IV food was tolerated so little that prescribed diet was a matter of no consequence. This patient has continued drinking but not as heavily or as early in the morning as previously.

NOTE: In the case of the hospital patient feeding was unsatisfactory on account of gastric symptoms before treatment was started. Following treatment the gastric symptoms disappeared and the appetite was good. This is the result to which we are accustomed in the treatment of pernicious anemia.

CONSIDERATION OF CASES OF PURPURA

There have been several cases showing purpura seen by you in the wards and we have discussed 2 cases in our conferences.

Purpura is seen as a symptom or episode in many conditions; in acute infections, particularly meningococcic infection, and in very severe attacks of the acute exanthemata, as measles, which with extensive petechiae is termed "black measles." In streptococcic septicemias petechiae commonly occur, and extensive extravasations may be seen. Injury to the capillary walls is probably the cause in these conditions. In advanced

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These terms are still in common use. Idiopathic is apt to be more and more narrowly restricted as time goes on.

There is only one type of purpura which really should be grouped as primary or idiopathic, that is—purpura hemorrhagica of Werlhof, or primary thrombocytopenic purpura.

In any reference to the purpura we are apt to find reference to Schönlein's disease or Henoch's purpura. Schönlein's disease or peliosis rheumatica or purpura rheumatica probably should not be considered as a disease entity. It designates a condition which may be acute rheumatic fever with a petechial eruption, or a purpura with joint extravasations. It is characterized by fever, joint swellings and pain and a characteristic petechial rash. It is probably a manifestation of streptococcal infection with widespread capillary damage and is a secondary or symptomatic purpura with joint involvement.

Cases in the earlier literature are variable in their characteristics including rheumatic fever with petechiae and even with exanthematous eruptions. Schönlein's original description is vague and inclusive of many conditions. There are, however, today cases of purpura showing a tendency to joint involvement which are termed Schönlein's disease.

Henoch's purpura also shows an indefinite picture, a purpura with a tendency to visceral extravasations giving pain and tenderness related to the affected region, and febrile reaction. This is probably a thrombocytopenic purpura in almost all instances and may be "primary," or there may be a demonstrated cause in which case it would be termed "secondary."

Any lengthy discussion of the symptomatology of Schönlein's or Henoch's purpura is not worth while. These were discussed at length when knowledge regarding rheumatic fever was even more scanty than it is today and when blood studies except as to the gross appearance of the clot were practically nonexistent. Most cases which would have formerly have been classed as Schönlein's disease would now be considered as rheumatic fever with eruption due to capillary damage, and some few as purpura with a tendency to joint extravasations. Most cases which formerly would have been called Henoch's purpura would now be classed as thrombocytopenic purpura

cardiovascular and renal disease purpura may occur probably from capillary damage by toxic influences as it usually occurs when the renal function is at a low ebb.

Purpuric extravasations are found as a result of damage to the blood by toxins, as snake venom, and by damage to the bone marrow by toxic substances, infectious diseases or malignant conditions directly invading the marrow and interfering with the production of normal blood elements.

In some purpuras the blood is found to be abnormal in some particulars, in other cases the blood shows no demonstrable fault qualitatively or quantitatively in its various elements, or in the properties of coagulation or as to bleeding time.

There is considerable confusion in the consideration of these cases due to lack of agreement in classification of the purpuras and lack of knowledge as to their etiology. The nomenclature is not clear in some regards and commonly employed terms are a little misleading in some particulars.

In references to purpura in older works the viewpoint and terminology will be very different from that employed by some writers today, but our knowledge is still insufficient to attempt a classification either exact or comprehensive. Let us consider the meaning of a few terms as ordinarily employed:

Purpura indicates a staining of the skin by extravasation of blood or blood pigment from the vessels into the tissues.

Purpura simplex indicates the occurrence of purpura without external hemorrhage from the mucous surfaces.

Purpura hemorrhagica indicates that bleeding mucous membrane exists as well as purpura and is also used to designate a supposed clinical entity, *idiopathic purpura hemorrhagica*, morbus maculosus or Werlhof's disease.

Symptomatic purpura means *secondary purpura*, i. e., that the purpura is a symptom of some recognizable disease or injury.

Idiopathic or *primary* is used in contradistinction to symptomatic or secondary. By this term is designated a purpura not secondary to a recognizable disease and particularly one in which can be shown abnormal conditions of the blood.

and following this the purpura and hemorrhages appeared. She showed a well-marked anemia and had apparently suffered sufficient hemorrhages to account for this. The blood count showed red blood cells 3,740,000, hemoglobin 75.6 per cent, white blood cells 3600, platelets 306,000. The spleen was markedly enlarged. The platelet count would seem to rule out thrombocytopenic purpura but her history showed that she had applied at another hospital for treatment last summer and when splenectomy was advised she left the hospital. Information from there showed a record of a very low platelet count—9/19/32, 64,000; 12/7/32, 18,000; 12/19/32, 75,000.

She went to another hospital where she was treated by radiation over the splenic area. Her platelet count was low at the beginning of treatment but rose later.

These patients showing a low count are subject to spontaneous remissions during which symptoms are apt to subside and the platelet count to rise promptly to normal. Following splenectomy the platelet count rises very rapidly and following radiation an increase may be expected.

This patient showed purpura hemorrhagica or thrombocytopenic purpura, probably idiopathic, or Werlhof's disease, and was seen in a remission which seemed to have been induced by radiation, at which time her platelet count was normal. She showed attacks of purpura, hemorrhages, and also evidence of visceral extravasations, one renal and another intra-abdominal, accompanied by pain and fever.

Splenectomy was advised but she left the hospital returning to the medical dispensary for observation. She died suddenly at her home last week, after exerting herself, probably from cerebral hemorrhage as there was evidence of sudden paralysis. The platelet count in the last week of her life was reported as 7000.

Case VI.—P. S., aged sixty-one, white, admitted 2/4/31. Discharged 5/18/32.

Before his recent admission to the medical wards, this man had previously been a patient in the neurological division of the hospital for a period of fifteen months, where he was diagnosed and treated as a case of primary pernicious anemia. The most striking feature of his previous admission was the extensive unexplained ecchymoses of the lower extremities, at one time involving the entire left leg, which quickly disappeared. It was also noted that on three occasions there had been sudden high temperature elevations which were preceded by chills. Moderate pain and tenderness were present at one time, but usually these reactions were unaccompanied by any other symptoms or local signs and

with a tendency to visceral extravasations. These might or might not be shown to be secondary or symptomatic.

Exudative or *allergic purpura* is a purpura associated with exudative lesions as urticaria angioneurotic edema or other lesions of this type. This class includes many cases of purpura with visceral and joint distribution.

Lack of platelets is a definite finding, and when purpura occurs with a low platelet count it is termed *thrombocytopenic purpura*. If no underlying conditions can be found to account for it the purpura is termed *primary*. Aside from the paucity of the platelets blood changes are not outstanding except for a secondary anemia which may be extreme in severe cases, and a failure in normal retraction of the clot, though the clotting time of the blood is not prolonged. The bleeding time is greatly lengthened. Idiopathic thrombocytopenic purpura or purpura hemorrhagica of Werlhof may be acute or chronic. The chronic type would better be termed "remittent" in many cases as the symptoms disappear and the blood picture may become practically normal between exacerbations.

The clinical picture in the chronic form shows repeated attacks with hemorrhages, petechial spots or extravasations, with fever and leukocytosis, and with sudden attacks of pain and tenderness in various parts of the body, particularly in the abdomen. The spleen is frequently found to be enlarged and may be intermittently very tender.

Treatment of this condition is unsatisfactory except by attack upon the spleen. Splenectomy seems to yield good results but the end-results are not demonstrated as this form of treatment has only been generally adopted during the past few years. x-Ray of the spleen area has been advocated but its advisability is open to question. Following splenectomy the platelets increase very rapidly and following x-ray treatment there may be a marked increase.

Case V.—Let us consider N. W., seen and discussed a few weeks ago. A woman, aged forty-eight, admitted to the Woman's College Hospital 2/11/33, gave a history of purpura and hemorrhages from the nose and gums occurring at various times for the past eleven months. She had pertussis in March, 1932,

teristic. The tongue is atrophic, achlorhydria is of long standing but the neurological symptoms are not altogether characteristic.

In secondary platelet deficiency the platelets may be formed in the circulation or spleen in normal amount and destroyed by some toxic factor, or it may be that the parent cells of the platelets, the megakaryocytes, are damaged by some toxic influence so that platelets are deficient in number or are imperfect and readily succumb.

Certain poisons, as benzol, may cause platelet deficiency, or bone marrow disease such as extensive malignant metastasis, leukemia, aplastic or pernicious anemia, may produce this result.

In this case we had the feeling that anemia of long standing had resulted in platelet deficiency. We find no definite toxic cause which can be assigned.

Dr. Custer has made a close study of the characteristics of the bone marrow in disorder of the bone elements. He has examined many specimens in cases of pernicious anemia, aplastic anemias, Hodgkin's disease, Banti's disease and purpura. He is definite in his view that this specimen indicates that the platelet deficiency is secondary in that the megakaryocytes are faulty in their appearance, being imperfect in structure and staining qualities. In primary purpura these cells are found to be normal in their appearance in stained sections and marrow smears. Dr. Custer suspects some toxic influence in that the marrow picture does not resemble that of advanced or untreated primary anemia. He tells us that, while the appearance of the marrow in such cases is characteristic, under treatment with liver or even in spontaneous remissions this characterization is lost. The patient having had considerable liver treatment in the past, it may, of course, be possible that primary pernicious anemia is the cause of the marrow fault and responsible for his purpura.

In a hospital with a well-equipped laboratory and a pathologist skilled in the study of marrow it seems decidedly worth

disappeared usually within twenty-four hours. He requested his release on 5/18/32 and was discharged against advice but in fair condition.

He was again admitted to the Philadelphia General Hospital on 2/25/33 on this service, complaining of spontaneous ecchymoses of lower extremities, which were preceded for several days by an "awful pain in the legs." No pain upon admission and no history of hemorrhages from any mucous surfaces. General weakness and slight dyspnea had been present for several months. No gastro-intestinal complaints.

Physical examination on admission revealed a well-nourished adult German, not acutely ill but quite anemic. Aside from a hypermature cataract of the left eye, emphysematous chest, and poor myocardial sounds, the examination was negative except for two large irregular purplish ecchymoses on medial aspect of both thighs, about 12 x 12 cm., indurated and with very little tenderness present. Blood pressure, 160/70. The neurological consultant, Dr. MacConnell, found only greatly diminished Achilles jerks without the usual cord changes of advanced or untreated pernicious anemia.

On admission, the initial blood count showed only 2,590,000 red cells, normal white cells and differential count; platelets 70,000 per cm.; normal bleeding and coagulation times. Blood serology, blood chemistry, and urinalyses were also essentially negative. Gastric analyses, with and without histamine hydrochloride, showed a persistent achlorhydria. This was also the case on the previous admission. After two weeks of generous liver diet supplemented by intramuscular liver injections and iron and ammonium citrate, the patient's nervous blood count had risen to 3,600,000 red cells and platelets to 150,000. The gastro-intestinal tract was negative from roentgenological standpoint.

About three weeks after admission, it was decided to have a sternal bone marrow biopsy taken. In the pathologic report, Dr. Custer says: "The marrow is approximately 30 per cent cellular; general structure unaltered; erythropoiesis is proceeding in normally active fashion; a distinct increase in the relative numbers of eosinophilic granulocytes as compared to the neutrophilic. In view of the purpuric symptoms, chief interest lies in the megakaryocytes; the nice degenerative-regenerative balance that normally exists is disturbed in favor of degeneration. Some of the cells are completely anuclear, the cytoplasm of the degenerate form is often hypergranular, sometimes vacuolated, and occasionally markedly fibrillar. One would consider an extraneous toxic influence in this case rather than a defect in the megakaryocytes per se. Diagnosis: Secondary purpura hemorrhagica."

There have been no recurrent vascular phenomena during this admission, the weakness largely disappeared and symptomatically the patient was so much improved that he was considered in fair condition for the combined cataract extraction operation and is now convalescing from this operation without any unusual bleeding.

This seems to be a case of thrombocytopenic purpura, which is secondary to or symptomatic of some other condition. The case seems like pernicious anemia but is not altogether charac-

while to avail ourselves of the valuable information which is derived from study of biopsy specimens of marrow.

The specimen is secured by a button taken from the sternum by trephining through the anterior plate and marrow of the gladiolus under local anesthesia. Fresh smears, sections of the fixed specimen, and sometimes cultures are studied. Sections of marrow from the tibia seldom yield satisfactory information.

possibilities in chronic bronchitis and early bronchiectasis before permanent structural changes have occurred in the bronchi and parenchyma of the lungs.

Practically all cases require bronchoscopic examination not only for foreign bodies but likewise for the removal of viscid secretions and plugs and indeed repeated bronchoscopic drainage alone has proved very beneficial in a large majority. Likewise frequent postural drainage and especially the elimination or drainage of foci of infection in the nasal accessory sinuses, mouth and tonsils. But while these measures along with various surgical procedures, a sanatorium regimen and the subcutaneous injection of autogenous vaccines are frequently helpful and indeed sometimes curative, yet it would appear that the possibilities of local disinfection and immunization are worthy of serious attention.

Naturally, a relatively large list of bactericidal agents is available for the choice of compounds to be employed, but it would appear that substances selected for attempted bronchial disinfection should possess the following essential properties:

1. A reasonably high degree of parasitidal activity *in the presence of pus* and especially for streptococci and staphylococci as likewise for other bacteria, spirochetes and fungi.

2. Be rapidly parasitidal because the time of contact must be necessarily brief.

3. Preferably stain the tissues in order to prolong antiseptic or bacteriostatic action.

4. Free of destructive effects for the bronchial cilia in order not to reduce or destroy their activity in the removal of secretions.

5. Possess the maximum degree of penetrability in order to reach and destroy micro-organisms entrenched in cells and tissues including the rich bronchopulmonary lymphatics.

6. Be free of injurious effects upon phagocytes in order not to interfere with phagocytosis which doubtless exerts a very important rôle in the mechanism of resistance and recovery.

7. Be free of injurious effects upon the pulmonary tissues. That is, the chosen antiseptic should not exert excessive hyper-

CLINIC OF DR. JOHN A. KOLMER

TEMPLE UNIVERSITY

BRONCHIAL DISINFECTION AND IMMUNIZATION

LAST week you were shown several cases representative of chronic suppurative pneumonitis including one of chronic bronchitis associated with suppurative sinusitis with early bronchiectasis as revealed by roentgenological examination following the installation of lipiodol, one of more advanced bronchiectasis likewise of the acquired type and presenting well-defined physical signs of this disease and one of abscess of the right lung. The etiology of these diseases was discussed with proper emphasis upon the frequency with which they are apparently secondary to primary infection of the upper respiratory tract. Your attention was also drawn to the fact that, aside from those due to congenital deficiencies of the bronchi and foreign bodies, the majority are apparently the result of infection with various types of streptococci with secondary infection by staphylococci, pneumococci and other organisms; that some cases of suppurative pneumonitis may be due to fuso-spirochetal infection and especially those characterized by bloody expectoration but that small numbers of fusiform bacilli and various spirochetes are to be regarded as secondary infection and largely responsible for the foul and fetid odor of the profuse expectorations so characteristic of these diseases, and so distressing to their unfortunate victims.

Today I wish to devote the clinic to a discussion of the treatment of these forms of suppurative pneumonitis with special reference to the possibilities of bronchial disinfection and immunization by the direct or topical application of chemical and biological agents and particularly to their therapeutic

possibilities in chronic bronchitis and early bronchiectasis before permanent structural changes have occurred in the bronchi and parenchyma of the lungs.

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7. Be free of injurious effects upon the pulmonary tissues. That is, the chosen antiseptic should not exert excessive hyper-

emia or inflammatory changes, abolish the cough reflex or interfere with ciliary action and bronchial peristalsis.

8. Be sufficiently low in toxicity to spare the kidneys, liver and other organs injurious effects following absorption from the lungs.

9. Furthermore the solution employed for irrigating the bronchi and preparing solutions of the chosen antiseptic should not favor the development of edema and especially since the tissues are already injured by infection.

Since the exudates in suppurative pneumonitis are usually plastic and so rich in coagulating principles as to coagulate solid or almost so in the Tucker, Clerf and other collectors employed in bronchoscopic drainage, it would appear advisable to employ a fluid possessing liquefying or digestive properties. For this reason the alkaline antiseptic like Dakin's solution command special attention but unfortunately some chemical antiseptics are precipitated by alkalis and the pulmonary tissues greatly irritated by concentrations sufficient for liquefaction of the exudates. It may be that proteolytic enzymes may be of service in this direction but so far we have not been able to work out a satisfactory solution of them for irrigating purposes.

Castex and Hardenreich¹ have reported favorably upon intrabronchial injections of neoarsphenamine in the treatment of spirochetic infections, and Stiehm,² the Ballons,³ Blumberg⁴ and others refer to the possible curative effects of intrabronchial injections of iodized oil (lipiodol) although the bactericidal activity of the latter is so low that it is possible that the benefit observed was due to other factors. Frazier,⁵ Glaser,⁶ Faulkner and Glaser⁷ have employed campiodol (iodized rape seed oil) for purposes of bronchography, and Jacobs and Dodies⁸ report that intrabronchial injections have proved an excellent aid in the treatment of bronchiectasis, but I have not studied its bactericidal properties. Jacobs⁹ has also reported favorably upon intrabronchial injections of 10 cc. of 1:5000 metaphen in oil at weekly intervals in the treatment of tuberculous cavitation and states that it has been found nontoxic and nonirritating while reducing the amount of expectoration, temperature, pulse and

respiration; Rudman and Ellison¹⁰ have employed metaphen in oil in the treatment of tuberculous pleuritis with effusions, reporting that it is apparently of value in the prevention of adhesions while proving highly bactericidal and well tolerated. Gomenol has been applied by Jackson, Tucker and others through the bronchoscope and apparently with some benefit, which is to be expected since this oil possesses some bactericidal activity as I shall discuss later on, but otherwise no systematic attempts at local disinfection appear to have been made although a number of antiseptics have been tried.

But even if the above requirements are fulfilled and I believe they may be by some antiseptics as discussed later on, *the important problem of adequate application to the infected tissues must be solved*. This refers not only to sufficiently wide distribution in the infected areas of the lungs along with adequate drainage of the secretions, but also and more importantly, *to sufficient frequency of application*.

Thus antiseptics may successfully reduce the number of pathogenic bacteria to some extent and otherwise fulfill these essential requirements, but bacteria escaping destruction soon begin to multiply under the favorable conditions of the lungs and the original state is soon restored unless a way and means for sufficiently frequent applications is worked out.

In other words *it would appear that but little or no benefit may result from an occasional application of a bactericidal agent*, for example once a week, by bronchoscopical application. Bronchoscopy is doubtless of great value in removing plugs of secretions and foreign bodies and is required occasionally for these purposes in the majority of cases, but it is necessary to employ a method permitting applications at frequent intervals, even daily, for a while at least, with the minimum of discomfort and expense to the patient. For this reason I am greatly interested in the possibilities of bronchial lavage as developed by Stitt,¹¹ Iglauder¹² and others and especially in the method of bronchoclysis for prolonged intrapulmonary therapy devised by Mandelbaum¹³ because they may afford a means of not only removing and washing out the purulent secretions

but provide a method of instilling relatively large amounts of bacteriostatic or bactericidal solutions for reaching areas beyond direct application through the bronchoscope. In other words, it would appear that but little is to be expected from the application of antiseptics on gauze pads through the bronchoscope because but small areas can be reached thereby and the time of contact with the infected tissues too brief, whereas if it were possible to introduce and leave relatively large amounts of antiseptic solution at frequent intervals a wider distribution and more prolonged contact may be secured with possible greater therapeutic benefit providing the procedure was found entirely safe and feasible.

Of course, the intravenous or intramuscular injection of chemotherapeutic agents of curative value would be the ideal in treatment, but there is nothing of proved value to employ by these routes of administration except neoarsphenamine or bismarsen¹⁴ for the treatment of Vincent's or other spirochetic infections of the lungs.

No doubt certain dangers may attend attempts at bronchial disinfection by the direct application and installation of antiseptics by bronchoclysis or bronchial lavage, and Mandelbaum states that bronchoclysis should not be used during the early or acute febrile stage of bronchopulmonary disease although he has found it to be a form of intrapulmonary therapy practically innocuous in thousands of instances in which his method has been used in human subjects. But it has already been shown by Stitt and others that 15 cc. of solution may be introduced with each inspiration. The cough reflex expels the solution along with the thick ropy secretions so that as much as 250 cc. may be used for cleansing purposes. Under the conditions at least some of the antiseptic remains for a while in contact with the infected tissues and according to my experimental work it is possible and safe to leave a portion of the last instillation for more prolonged bactericidal and bacteriostatic action without local and general injury.

The question of spreading the infection to healthy portions of the lung is very important in this connection, but if bacteri-

TABLE 1
BACTERICIDAL TESTS

Compound.	Highest bactericidal dilution in five minutes.	
	For <i>Streptococcus hemolyticus</i> .	For <i>Staphylococcus aureus</i> .
Gentian violet.....	1 : 6,000	1 : 4,000
Neutral acriflavine.....	1 : 6,000	1 : 3,000
Equal parts of gentian violet and acriflavine.....	1 : 6,000	1 : 4,000
Rivanol.....	1 : 3,000	1 : 1,500
Merodicein.....	1 : 10,000	1 : 5,000
Mercurochrome.....	1 : 200	1 : 100
Mercurophen.....	1 : 20,000	1 : 15,000
Metaphen.....	1 : 30,000	1 : 60,000
S.T. 37 (1 : 1000 hexylresorcinol).....	1 : 3	1 : 2
Potassium permanganate.....	1 : 175	1 : 75
Argyrol.....	1 : 100	1 : 20
Gomenol.....	1 : 60	1 : 8
1 per cent iodine in 25 per cent alcohol.....	1 : 75	1 : 75
Dakin's solution.....	1 : 30	1 : 4
Chloramine-T.....	1 : 600	1 : 400
Dichloramine-T.....	1 : 300	1 : 75
Lipiodol (iodized oil).....	None	None
Neoarsphenamine.....	1 : 50	1 : 30

TABLE 2
SPIROCHETICIDAL TESTS

Compound.	Approximate concentration sufficient to cause loss of motility in five minutes.
Gentian violet.....	1 : 100
Neutral acriflavine.....	1 : 300
Rivanol.....	1 : 300
Merodicein.....	1 : 25
Mercurochrome.....	1 : 50
Mercurophen.....	1 : 1000
Metaphen.....	1 : 1000
S.T. 37 (1 : 1000 hexylresorcinol).....	Undiluted
Potassium permanganate.....	1 : 25
Argyrol.....	1 : 10
Gomenol.....	1 : 10
1 per cent iodine in 25 per cent alcohol.....	1 : 5
Chloramine-T in water.....	1 : 5
Neoarsphenamine.....	1 : 50

1:25 solution and bronchial secretions containing large numbers of various spirochetes (final dilution 1:50) showed complete loss of motility within five minutes as determined by dark-field

evidences of general toxicity with special reference to possible injury of the kidneys.

The preliminary bactericidal tests were conducted with a strain of hemolytic streptococcus and *Staphylococcus aureus*. While the value of these tests is limited, yet by conducting them in a menstruum rich in protein at body temperature, the results are not without significance in the selection of compounds for intrabronchial disinfection.

The technic employed was very simple, as follows: (1) To 90 cc. of sterile ascites fluid was added 10 cc. of a twenty-four-hour broth culture of the test organism and 2 cc. amounts placed in sterile test tubes. (2) Solutions of each chemical compound were prepared in physiological saline solution and varying dilutions added in amounts of 2 cc. each. Under these conditions the bactericidal action of each compound was determined for relatively large numbers of the organisms in a 50 per cent dilution of ascites fluid representing a large amount of protein approximating the conditions of inflammatory exudates. (3) These mixtures were kept in a water bath at 37 C. and subcultured at the end of five minutes in order to select substances on the basis of fairly rapid bactericidal action.

The substances tested and the approximately highest dilutions completely bactericidal for the two organisms at the end of *five minutes* are shown in Table 1.

Since spirochetes are not infrequently found in the exudates of chronic bronchitis, bronchiectasis and other types of suppurative pneumonitis, it was necessary to inquire into the spirochetical activity of at least some of the bactericidal agents listed in Table 1 in relation to bronchial disinfection, even though the exact etiologic status of these organisms is as yet unsettled except in some instances of pulmonary spirochetosis where such enormous numbers of spirochetes are found in the profuse exudates as to leave little or no doubt of their etiologic significance.

As shown in Table 1 neoarsphenamine was completely bactericidal for *Streptococcus hemolyticus* and *Staphylococcus aureus* in dilutions of about 1:50. Mixtures of equal parts

By reference to Table 1 it is observed that these maximum tolerated dilutions were bactericidal for the streptococcus and staphylococcus with the exception of S.T. 37, potassium permanganate and lipiodol. With several however, the maximum tolerated dilutions were slightly higher than the bactericidal dilutions as in the case of the dyes (gentian violet, acriflavine and rivanol), mercurochrome, argyrol, gomenol, Dakin's solution, chloramine-T, dichloramine-T and neoarsphenamine, whereas merodicein, mercuraphen, metaphen and the iodine solution were tolerated in dilutions three to twelve times stronger than their bactericidal dilutions. From this standpoint the last mentioned would appear to be preferred for bronchial disinfection but a final decision upon the choice of compounds was based upon gross and histologic examinations for possible evidences of pulmonary irritation.

For this purpose autopsies were conducted on all animals either immediately after death or twenty-four hours after receiving the last intratracheal injection of solutions of each compound.

At least three to six rabbits were used for each compound and the examinations conducted after injecting intratracheally from two to twenty-four doses of 1 cc. per kilogram of weight.

Sections of the trachea were made just above the bifurcation into the primary bronchi. Sections of the lung were selected from areas showing the maximum macroscopical changes and sections were also made of both kidneys.

Marked variations were observed in individual animals. For example, an animal receiving three injections sometimes showed more pronounced histologic changes in the trachea, bronchi and lungs than a second animal receiving twelve injections of the same substance at the same time and in the same dosage. Furthermore, the changes produced in the lungs were more or less localized rather than diffused; as a general rule the greater changes occurred in the right lungs, especially around the primary bronchus and the lower rather than the upper lobes. Sections were always taken from the most injured portions for histologic study.

examination. Of course this does not necessarily imply the death of organisms but it is likely that under the conditions the majority at least were crippled and probably destroyed.

Additional tests with other chemical agents are shown in Table 2. As a general rule the finer spirochetes (*presumably Sp. microdentium*) were more easily destroyed than the larger and coarse ones like *Sp. macrodentium*. It was surprising however that the final concentrations of various agents required to cause complete loss of motility of spirochetes in purulent secretions within five minutes were many times greater than required for bactericidal activity by the method employed. For example, gentian violet, acriflavine and rivanol were spirocheticidal in 1:100 to 1:300 but bactericidal in 1:3000 to 1:6000; merodicein was bactericidal in 1:5000 to 1:10,000 but spirocheticidal in only 1:25; mercurophen and metaphen were bactericidal in 1:15,000 to 1:60,000 but spirocheticidal in only 1:1000, etc.

In so far as the maximum tolerated doses of the various compounds employed are concerned, it would appear that the following represent the approximate dilutions in dose of 1 cc. per kilogram of weight every two days for six to twenty-four injections:

Gentian violet	1: 2000
Neutral acriflavine	1: 2000
Equal parts of these	1: 2000
Rivanol	1: 2000
Merodicein	1: 800
Mercurochrome	1: 300
Mercurophen	1: 5000
Metaphen	1: 5000
S.T. 37 (1: 1000 hexylresorcinol)	1: 2
Potassium permanganate	1: 1000
Argyrol	1: 20
Gomenol	1: 10
1 per cent iodine in 25 per cent alcohol	1: 25
Dakin's solution	Undiluted
Chloramine-T in water	1: 300
Dichloramine-T in chlorozan	1: 200
Lipiodol (iodized oil)	Undiluted
Neoarsphenamine	1: 50

prolonged disinfection, would be without injurious effects at the rate of a treatment every two days or twice a week:

Gentian violet	1: 2000	
Acriflavine (less irritating than gentian violet)	1: 2000	
Merodicein	1: 2000	
Mercurophen or metaphen	1: 5000	
S.T. 37 (equal parts or S.R. 37 solution and saline) ...	1: 2000	
Potassium permanganate	1: 500	to 1: 1000
Argyrol	1: 20	
Gomenol	1: 10	
Chloramine-T	1: 300	
Neoarsphenamine	1: 50	

Mercurochrome 1:200 is apparently too irritating and may produce renal injury; a 1:25 dilution of a stock 1 per cent solution of iodine in 25 per cent alcohol also produced pulmonary changes as was likewise true of Dakin's solution. It is to be observed that lipiodol (iodized oil) was well tolerated in confirmation of the work of Stiehm and the Ballons, but is too low in bactericidal activity to be used for bronchial disinfection.

It would appear therefore that bronchial disinfection may be attempted in the treatment of bronchiectasis and other types of "suppurative pneumonitis" by lavage or bronchoclysis with disinfectant solutions. If lavage is employed, 15 cc. amounts may be slowly passed through into the main bronchus coincident with each inspiration, followed by expulsion of the solution together with the thick ropy secretions by the cough reflex, until as much as 100 to 250 cc. have been used for lavage according to the principles of the Stitt-Wooding method. Following the last lavage I believe that it will be safe to leave 15 cc. in the bronchi for a wider distribution and more prolonged bactericidal action.

Since frequency of application is undoubtedly a matter of primary importance, I hope that it will be possible to apply the treatment at daily intervals, in some instances for several days at least, followed by subsequent treatments every two days or several times a week according to conditions. This is a matter, however, to be determined by clinical experience; all that I have hoped to show by the work summarized in this paper is that

As expected the bronchi have shown much more evidence of injury by all compounds than the trachea. Indeed, with but few exceptions all of the compounds employed have produced some injury of the lungs, although in this connection it should be emphasized that the doses were quite large and amounted to 1 cc. per kilogram every two days corresponding to as much as 60 to 70 cc. for an adult human of average weight. Furthermore, it is to be remembered that all was left in the lungs after each injection rather than only a small portion. But I have purposely made the conditions very severe in order to elicit the maximum injury.

With few exceptions all of the compounds were well borne by the trachea although the majority produced irritation of the bronchi and especially the smaller branches; this was especially true in the case of those rabbits receiving six to twenty-four injections at two-day intervals. As a general rule, these bronchial changes were of mild degree and largely in the nature of hyperemia with some edema of the submucosa, although in some instances bronchial exudates of fibrin and polymorphonuclear leukocytes were produced.

As expected the predominant lung changes were in the form of peribronchial areas of hyperemia, edema and slight leukocytic infiltrations of the alveoli. Indeed, practically all compounds produced such lesions and especially in the case of those animals receiving more than six injections at two-day intervals. In some instances, however, these changes were quite severe with relatively large areas of pneumonitis and multiple abscesses, as in the case of a large number of injections of mercurochrome, hexylresorcinol, iodine and the chlorine compounds.

As a general rule, there were none or but slight evidences of renal irritation and such as were found occurred only among rabbits receiving six or more injections.

However I believe that it is entirely likely that lavage of the bronchi of humans with 15 cc. amounts of the following solutions for a total of 250 cc. and leaving the last 15 cc. in for

by intrabronchial injections of vaccines, antiviral and bacteriophage may offer even greater therapeutic possibilities and also prove worthy of clinical trial in the treatment of bronchiectasis and other types of pulmonary suppuration.¹⁶

Undoubtedly subcutaneous and intracutaneous injections of properly prepared autogenous vaccines are sometimes of therapeutic value in certain cases of chronic bronchitis, especially those associated with allergic asthma, but vaccine therapy has generally failed to be of any particular value in the treatment of bronchiectasis.

Phagocytosis is undoubtedly the chief mechanism of defense against bronchial infection and likewise the chief and possibly the sole mechanism of recovery. Therefore, anything that may safely be done to increase phagocytosis of the organisms productive of chronic bronchitis and bronchiectasis, and especially of streptococci and staphylococci, may be expected to have therapeutic value.

In this connection I refer not only to phagocytosis of organisms by microphages (the polymorphonuclear leukocytes) but likewise, and possibly more importantly, to phagocytosis by macrophages with special reference to clasmatocytes. At least the cells of the macrophage system appear to be more phagocytic in chronic infections.

As shown by Gay and Morrison, the intrapleural injection of sterile broth, 1 per cent egg white, 1 per cent peptone solution, acacia broth and other substances into the pleural cavities of rabbits has resulted in a great increase in these clasmatocytes in the exudates and pleural tissues, and after seventy-two hours the changes resulted in greatly increased resistance to intrapleural injections of virulent streptococci. According to these investigators, however, the results were not due as much to what was injected as to the time element, and it has occurred to me that intrabronchial injections of vaccines made of heat-killed broth cultures of streptococci and other organisms may serve equally well in producing a local mobilization of these and other phagocytic cells.

Furthermore, it may be that a vaccine administered in this

it would appear possible to safely employ a number of compounds in solutions of sufficient bactericidal activity along with the removal of purulent exudates by lavage as part of a program for the treatment of at least some cases of "suppurative pneumonitis."

From the standpoint of choice of compound no one has stood out predominantly among those employed in this study. But it would appear that the following are worthy of trial from the standpoint of bactericidal and spirocheticidal activity and freedom from toxic effects, although their influence upon bronchial cilia has not yet been determined:

- (a) Equal parts of 1: 2000 gentian violet and 1: 2000 acriflavine.
- (b) Mercuraphen or metaphen, 1: 5000.
- (c) Merodicein, 1: 2000.
- (d) Equal parts of hexylresorcinol solution 1: 2000 (S.T., 37) and saline solution.
- (e) Argyrol, 1: 20.
- (f) Chloramine-T, 1: 300.
- (g) Neoarsphenamine, 1: 100 for spirochetic infections.

Each compound may be prepared with saline solution and the chosen solution should be warmed to about 40 C. before administration.

According to my results these compounds in the strengths mentioned are bactericidal in the presence of pus, do not destroy leukocytes or retard phagocytosis, appear to otherwise fulfill most of the requirements of an ideal antiseptic as previously outlined, and will probably be well borne by humans, although the latter must be determined by clinical experience as likewise a final choice of the compound to employ.

BIOLOGICAL THERAPY APPLIED TO BRONCHIAL DISINFECTION

Therefore while bronchial disinfection by intrabronchial lavage with various chemotherapeutic agents would appear to be both possible and safe and worthy of clinical trial in the treatment of bronchiectasis and other types of chronic suppurative pneumonitis, local immunization and disinfection of the bronchi

from intrabronchial injections of bacteriophage in the treatment of chronic bronchitis and bronchiectasis.

At the outset, however, it was realized that bacteriophagic therapy involved considerable technical difficulty, especially in the preparation of suitable and potent bacteriophage for the streptococci recovered in cultures of bronchial secretions. Staphylococcus bacteriophage is easier to prepare, and that which is commercially available is frequently lytic for the staphylococci occurring in purulent bronchial exudates, but the preparation of phage for pneumococci has met with no success so far in my laboratory.

Vaccines of *Staphylococcus aureus* and hemolytic streptococci recovered in cultures or bronchial secretions, containing approximately 1,000,000,000 heat-killed cocci per cubic centimeter and preserved with 0.3 per cent cresol, were extremely well borne by rabbits receiving as much as 1 cc. per kilogram of weight every two or three days for as many as twenty-four consecutive intrabronchial injections. In every instance the animals survived, maintained their weight and showed no demonstrable ill effects to either vaccine.

The same is true of a second series of rabbits receiving from six to twenty-four intratracheal injections of antiviruses of the same strains prepared by cultivating the organisms in a broth medium for ten days followed by Berkefeld filtration. As much as 1 cc. per kilogram of weight was injected every two or three days, and all animals survived without demonstrable ill effects.

Similar results were observed with bacteriophages for both strains injected intratracheally in a similar dose of 1 cc. per kilogram of weight every two or three days for a total of from six to twenty-four consecutive injections, so that it may be stated that these substances were well borne by normal rabbits by this route of administration despite the fact that the doses were purposely made extremely large according to body weight. It is true that the injections were sometimes followed in a few hours by a temporary elevation of rectal temperature along with slight but definite leukocytosis, especially in those animals receiving intrabronchial injections of the two vaccines, but these

manner may cause increased production of antibodies, with special reference to opsonins, by the local tissues (bronchi and parenchyma of the lungs), since it would appear that some evidence has accumulated to show that antibodies are produced primarily and principally by the tissues directly infected and antigenically stimulated. And since opsonins bear an important and essential relationship to the mechanism of phagocytosis, it has occurred to me that intrabronchial injections of autogenous vaccines prepared with broth may serve the dual purpose of increasing the macrophages of the exudates and tissues with special reference to clasmatoocytes, along with an increased production of specific opsonins so vitally concerned in both microphagic and macrophagic phagocytosis.

In this connection it is also pertinent to inquire into the possible therapeutic value of intrabronchial injections of Besredka's antiviral in the treatment of chronic bronchitis and bronchiectasis since this may be related in some respects to the artificial stimulation of clasmatocytic phagocytosis.

Antiviral is prepared by cultivating the organism in a suitable broth medium for from eight to ten days followed by Berkefeld filtration. The filtrate is designated as "antiviral," and according to Besredka contains something which is specifically bacteriostatic and bactericidal for the organism. That is to say, if the organism is replanted in the filtrate it either fails to grow or grows but sparsely, whereas other organisms grow almost as luxuriantly as in the control of broth medium. Besredka stated that the inhibiting substance is specific, thermostable and atoxic and for the want of a better term has called it "antiviral."

Personally, I am inclined at present to the view that antiviral owes its therapeutic properties to stimulation of both microphagic and macrophagic phagocytosis along with local antibody production, but it may contain a principle directly destructive for the organism as Besredka maintains. If this is true, there may be a relationship between antiviral and bacteriophage and at all events it would appear profitable likewise to inquire into the possible therapeutic benefit to be derived

bronchial injections of the pneumococcus vaccine and antiviral. For example, the intratracheal injection of 0.5 cc. of ten-hour hormone broth cultures of this pneumococcus into control rabbits resulted in a fatal septicemia of all with positive cultures of the heart blood within forty-eight hours after inoculation. The same was true of rabbits inoculated intratracheally after receiving from two to three intrabronchial injections of sterile broth, indicating that the broth alone was without demonstrable protective value against this highly virulent pneumococcus by intratracheal injection. But all of the animals receiving the intrabronchial injections of the vaccine survived when given injections with the virulent pneumococcus, as was likewise true of all animals receiving three injections of the antiviral. These results, therefore, afforded definite evidence of the fact that intrabronchial injections of type I pneumococcus vaccine and antiviral resulted in immunization against fatal infection by intratracheal inoculation with the organism, and since intrabronchial injections of sterile broth were without these effects it is apparent that the presence of the pneumococcus and its products in the vaccine and antiviral produced specific effects.

Less definite evidence, however, was secured in the case of the staphylococcus and streptococcus owing to the fact that both organisms were much less virulent for rabbits by intratracheal inoculation.

Only from 20 to 50 per cent of the controls inoculated intratracheally with large amounts of twenty-four-hour hormone broth cultures (2 cc.) succumbed with septicemia, as was likewise true of controls receiving three preliminary intrabronchial injections of sterile broth for nonspecific mobilization of microphagic and macrophagic phagocytes including clasmatoocytes. However, all animals receiving three preliminary intrabronchial injections of the staphylococcus and streptococcus vaccines and antiviruses survived when inoculated intratracheally with 2 cc. amounts of twenty-four-hour hormone broth cultures of the respective organisms and thereby indicated some degree of acquired immunity; but since some of the controls likewise

changes were usually observed only after the first one to three injections, following which it appeared that the animals rapidly acquired a tolerance for all three products of each organism.

Furthermore, the injections did not appear to produce more than slight amounts of bronchial exudates. Autopsy was performed several days after the last of six, twelve and twenty-four injections of each product, and the lower portion of the trachea and bronchi were carefully inspected along with the preparation of smears from numerous locations for cytological examination, but in no instance were there any macroscopical evidences of pronounced bronchitis resulting from irritation due to any of the products administered.

The smaller bronchi, however, frequently contained more exudate than was found in untreated controls and especially in those rabbits receiving intrabronchial injections of the two vaccines; smears stained with methylene blue (methylthionine chloride, U.S.P.), hematoxylin and eosin and neutral red showed the presence of increased numbers of not only polymorphonuclear leukocytes but likewise of the larger cell corresponding to descriptions of the morphological and staining characteristics of clasmatoocytes. These cytological changes were most marked, however, in smears of secretions from rabbits receiving injections of the vaccines and antiviruses, but were practically absent or much less in evidence in smears taken from animals receiving the injections of the two bacteriophages.

Furthermore the results have clearly shown that intrabronchial injections of staphylococcus and streptococcus vaccines, antiviruses and bacteriophages result in the production of specific opsonins and agglutinins in normal rabbits.

Additional experiments were now conducted in an attempt to determine if intrabronchial injections of vaccines and antiviruses of virulent *Staphylococcus aureus*, a hemolytic streptococcus and a type I pneumococcus afforded any protection against intrabronchial injections of broth cultures of these organisms.

Especially definite evidence of acquired immunity of the type I pneumococcus was observed after as few as three intra-

or other collectors and cultured in flasks of hormone broth medium suitable for the cultivation of streptococci. These may be incubated for about five days, at the end of which time fairly heavy growths will be observed. In many instances these are almost pure cultures of streptococci, but in the majority of such cultures staphylococci, pneumococci and various gram-positive and gram-negative organisms also occur with streptococci predominating. The mixed culture, however, should be used and may be diluted with sterile saline solution to give a total concentration of about 1,000,000,000 organisms per cubic centimeter. Cresol may be now added to give a total concentration of 0.5 per cent (10 cc. of a stock 5 per cent solution to each 100 cc. of vaccine), well mixed and incubated at 37 C. for twenty-four hours when subcultures are made for sterility. This type of vaccine contains the broth and approximately 1,000,000,000 chemically killed organisms per cubic centimeter along with their exogenous toxins, and, in my opinion, is to be preferred to the usual heat killed suspensions in saline solution in order to secure the effects of the broth alone in the mobilization of both microphages and macrophages with special reference to clasmotocytes in both the bronchial exudates and bronchial tissues for purposes of phagocytosis.

Antivirus may be prepared in exactly the same manner, except that the culture of bronchial secretions in broth is cultivated at 37 C. for ten days followed by Berkefeld filtration. The clear filtrate should be then cultured for sterility and put up in sterile vials or flasks in the amounts required for treatment without the addition of a preservative.

Only future clinical trial can determine the relative therapeutic effectiveness of vaccine and antivirus; personally, I expect results from both and especially from the latter.

The method of administration and dosage must be likewise determined by clinical trial and experience, but I would suggest that the ropy, mucoid secretions be first removed by lavage before introducing vaccine, antivirus or bacteriophage. According to this method, 15 cc. of saline solution is slowly forced through a catheter into the bronchi coincident with each

survived, the results were not as definite as those observed with the type I pneumococcus.

However, it was apparent that as few as three intrabronchial injections of vaccines and antiviruses of *Staphylococcus aureus*, a hemolytic streptococcus and a type I pneumococcus resulted in engendering demonstrable degrees of acquired immunity to the three organisms which was especially well marked in the case of the pneumococcus.

I am convinced, therefore, that the safe and reliable use of intrabronchial injections of vaccines, bacteriophages and bacteriophages in the treatment of the chronic and acute bronchitides, bronchiectasis and other types of bronchopneumonitis of man.

Certainly it would appear from these experiments that all three substances are sufficiently well tolerated by the bronchial injection and that their administration may be of therapeutic benefit.

Autogenous vaccines and bacteriophages are especially well adapted in this connection because of the ease of preparation and the large amounts likely to be required. The preparation of bacteriophage is much more difficult and indeed not so feasible for some of the bacteria common to human bronchopneumonitis. *Staphylococcus bacteriophage* is relatively easy to prepare and may be obtained in considerable quantities. The preparation of streptococcus and pneumococcus bacteriophages is more difficult and indeed impossible as far as the preparation of the large amounts of actively lytic proteins are concerned. Furthermore, bacteriophages should not be used until preliminary tests have shown that they are active against the organism in the organism against which they are to be employed. I believe that intrabronchial injections of actively lytic bacteriophages may be of therapeutic benefit in the treatment of bronchopneumonitis. The preparation may constitute an objection to their use on a large scale.

Autogenous vaccines, however, are readily prepared in large amounts, and for this purpose a method for obtaining secretions by secured bronchoscopy in the throat, which

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inspiration, followed by expulsion along with the thick ropy secretions until as much as 250 cc. is used. Following the last washing, the vaccine, antiviral or bacteriophage may be introduced.

The initial dose may be about 5 cc. in order to have it retained with as wide distribution as possible. If well borne, the treatments may be given about twice a week and the doses gradually increased. Larger doses are particularly indicated if bacteriophage is employed. It may be that the doses of vaccine and antiviral must vary for individual cases according to the amounts of toxin present, since it is likely that both contain variable amounts of toxins which will vary with different cultures, especially in the cases of streptococci and staphylococci.

When vaccine or antiviral are employed there may be an added advantage in using one of the chemical disinfectants for lavage as suggested above instead of the plain saline solution. Indeed, this would appear to be the better procedure in order to secure the possible benefit of chemical disinfection, especially since the disinfectants and solutions recommended are without injurious effects on the bronchi and phagocytes; but if bacteriophage is employed, the disinfectants should be omitted in the lavage because they may destroy the phage if the latter is indeed a living virus.

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The symptoms and signs of early infection differ in children and adults in that joint involvement is extremely rare and sweats practically never occur. Generalized pains—"growing pains"—or aches must be regarded with grave suspicion especially when associated with low-grade fever or rapid pulse or perhaps a slightly enlarged heart and roughened mitral first sound. The popular belief that tonsillectomy prevents heart disease or recurrent attacks of rheumatic infection or its symptoms, notably chorea, is fallacious clinically and pathologically. The removal of these first lines of defense is dependent entirely upon whether they have been completely destroyed by infection—any infection—and are therefore functionally useless.

Take for instance the case of F. W.:

Aged four years. She developed anorexia, lassitude, generalized aches, and a roughened first sound at the apex. Three months after the subsidence of her first attack her tonsils and adenoids were completely removed. One year later, the next spring in fact, she had another attack, more marked than the first, to be followed by an attack of chorea when she was six years of age.

Again, removal of the tonsils and adenoids before rheumatic infection has put in an appearance is not a prophylaxis, as this case illustrates:

G. Y. at five years of age had had his tonsils and adenoids removed. At ten years of age he had a fever, joint pains, and enlarged heart with a systolic murmur at the apex. He subsequently had two other attacks but because of rigorous treatment including long periods of rest in bed, salicylate of soda, and regulated activity when ambulatory, his murmur has disappeared. His activities are those considered normal for a high school boy. He now lives in Arizona where he has no further attacks.

Some retain their tonsils and recover:

R. H., aged six, had rheumatic fever with a mitral murmur at the apex. He had three attacks before puberty. His treatment was the same as that of G. Y. except that he stayed in Philadelphia. With graduated increase in exercise his heart has stood the test of college baseball and at thirty-five years of age he obtained without extra premium life insurance for one hundred thousand dollars. He still has his tonsils which are atrophied but unscarred surgically.

The use of salicylate of soda with bicarbonate of soda is as near a specific as any suggested remedy for rheumatic infection.

CLINIC OF DR. EDWARD L. BAUER

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HEART DISEASE PREVENTION VERSUS HEART SALVAGE

HEART disease prevention is a problem of the general practitioner and the pediatricist. A definition of heart disease prevention can be succinctly stated as the prevention of serious damage by infection to the heart muscle, valves, pericardium, and functional control system. This attacking infection is generally rheumatic, diphtheritic, or scarlatinal, but some other infections of lesser frequency may occur. Rheumatic infection is by all odds the most common.

To prevent heart disease or heart damage therefore one must prevent or adequately control infections likely to attack the heart. Once damage is done the problem is one of salvage and not of prevention.

Prophylaxis in rheumatic infection is largely a public health function because it is primarily a mass and not an individual problem. It is a problem of housing and sanitation, ventilation, air conditioning, and heating. The individual physician enters into the problem by joining aggressively in the educational training to control or correct faulty habits of living, exercise, diet, and dress. It also places the burden of early recognition of infection upon his shoulders and the adequate management thereof.

It must be remembered that rheumatic infection is a generalized infection involving the heart as well as other organs and tissues, and that heart involvement is not therefore a sequel to but a part of the disease. Many portals of entry must not be confused with foci of infection that are distributed throughout the body as submiliary nodules.

difficult is heart salvage from the economic and mortal standpoints.

H. D., aged thirteen years, presented himself to the Cardiac Clinic at the Jefferson Hospital with the following history. Headaches, pains in joints, shortness of breath on exertion, and lassitude were the symptoms. Five years previous to this visit he had had a severe attack of rheumatic infection and had been kept in bed for six months. He seemed well but did not have adequate ambulatory care or observation thereafter for several "minor" attacks were ignored and no rest in bed followed.

He now has a heart enlarged to the right and left, diffuse apical impulse, presystolic thrill and systolic shock at the apex, and an impulse in the vessels of the neck. He has diastolic and systolic murmurs at the apex and a soft diastolic murmur over the aortic area transmitted into the neck. Surely this is a problem of heart salvage to tax the ingenuity of the cardiologist.

Here the valves have become fibrotic and vegetations have probably added to the difficulties. The myocardium has not recovered its former self and is not likely to do so, at any rate not completely. However what is left must be developed and conserved. One asset is youth. This means growth and reparation. On the other hand puberty in either sex will in itself demand a heavy toll on the resources of the child. Puberty is always a trying period for the heart conservator.

Cardiac irregularities are generally of little significance in the child's heart. Frequently sinus arrhythmia will occur especially during the convalescing period following acute infections. Recovery is the rule, especially if rest and adequate hygiene are provided. Occasionally heart block will occur during rheumatic infection in childhood as is evident in the following history.

C. M., born January 27, 1920, was referred to the Jefferson Hospital Children's Clinic in December, 1926, by a school physician because the child had a "bad heart and was nervous." The patient had had an attack of "rheumatic fever" when four years of age but, according to the father, no subsequent attacks. His treatment at the time was meager according to our standards. His tonsils had been removed one year previous to his admission to our clinic. The child was chicken breasted (old rickets). His heart was enlarged particularly to the left. The left border reached the anterior axillary line down to the sixth rib. The right border was 3 cm. to the right of the midsternal line. The apex beat was heard in the fifth interspace at the anterior axillary line. There were heard diastolic and systolic murmurs at the apex and the third interspace to the left of

This drug in large doses must be given with the patient at rest. Just as important, however, is gradually increased but carefully regulated exercise before resuming the activities of normal living. This technic and results can be illustrated by the case of M. A. M., aged ten years:

This girl was a large child, strongly knit. She had an attack of rheumatic fever following a sojourn in a northeastern summer camp with its undue damp exposure. She was sick for two weeks or more with generalized aches, an afternoon temperature of 102 F., lassitude, and loss of appetite. Her heart was enlarged to the left and a faint systolic murmur was heard at the apex transmitted well out into the axilla. Her wrist pulse was 130 per minute. For weeks after her clinical picture had subsided under rest, sodium salicylate and sodium bicarbonate $\bar{a}\bar{a}$ grains xv q.i.d., she had a wrist pulse persistently found at 120 per minute. Her heart murmur disappeared and a good muscle tone returned. When her wrist pulse reached 90 per minute passive massage was commenced and her pulse watched. It was not affected. When it returned to 70 per minute gradual exercise was permitted. First a few steps to a chair, then longer distances until she could go up and down stairs. The pulse was used as a guide because the heart showed no dilatation. If the pulse had not returned promptly to normal following effort, further rest would have been indicated. Salicylate of soda and syrup of the iodide of iron were alternated weekly throughout convalescence. She became an expert horsewoman, and at twenty years of age gave birth to a baby boy with no difficulty whatever. She has no evidence of heart disease.

Certain pathologic factors must be visualized to make clear an understanding of the possibilities of return to normal function of the heart in rheumatic infection. The enlargement of the heart is due to the dilatation of the musculature and A-V rings permitting of roughening or "muffling" of the muscular quality of the first apical sound. A regurgitant murmur may also occur. This is not due to endocarditis as is generally interpreted but to myocardial degeneration. Still later when the valves are involved the connective tissue is more apt to be affected causing stiffness resulting in stenosis. Valvulitis not endocarditis is the actual pathology. This picture strengthens the position of heart disease prevention as the function of the clinician in the early days of infection. Should his part be neglected either because of his dereliction or failure of patient or family cooperation, disaster will result. The mortality tables verify this and the following cases show clearly how

led to believe? It is true that the general run of defective hearts involving the bad prognostic sign of cyanosis cannot be reasonably expected to show a reserve sufficient enough to assume the added burden of infection. However, it occasionally happens that such is the case, as the history of A. V. will attest:

This child was born in September, 1920. He has been cyanotic since birth and has become more so since he has grown older. He has had frequent attacks of tonsillitis and when ten years of age had a marked rheumatic infection that was evident from time to time until the present writing. He also had a severe attack of scarlet fever two years ago.

The child is deeply cyanotic and has marked clubbing of the fingers. He has a systolic murmur at the apex transmitted into the axilla, a systolic pulmonary murmur, and a to-and-fro murmur in the third interspace, left side (patent ductus arteriosus). His heart is enlarged to the left and right. He also has a marked ricketic deformity of the chest. In all, the congenital picture is sufficient to justify a distinctly unfavorable prognosis so that the superimposed infection together with the nutritional and hygienic handicaps should have been his nemesis.

These brief histories have been given shorn of unnecessary detail in order to bring out the difference between heart disease prevention and heart salvage. This is important because heart disease prevention can be practiced and should be kept uppermost in mind in dealing with heart disease. Salvage is equally important in those where neglect or at least inattention has permitted infection to obtain its devastating foothold. There is no gainsaying the fact, however, that it is the more difficult task and in most instances less satisfactory in its ultimate results.

It is important to realize the environmental, climatic, and hygienic influences that encourage infection and handicap the infected. Damp and foggy weather, especially near the seacoast, adds to the hazards of the susceptibles. England is the greatest sufferer and in America the early spring, which most nearly approaches the English climate, finds our greatest incidence, especially along the northeastern and middle Atlantic seaboard.

Housing and other hygienic factors abet infection. The greater number of cases are found among the poor and those just over the poverty line. Even the lovers of the great outdoors may succumb as is evident in the high incidence among

the sternum. The auricular rate was 70 per minute and the ventricular note 54 per minute.

For three years this picture remained unchanged. The patient seemed to grow and responded to activities with reasonable restriction. In the fourth year, with no change in the physical picture, the child had attacks of syncope on the slightest provocation. These attacks stopped with the advent of complete heart block. An electrocardiographic study made by Dr. Ross V. Patterson is as follows: "An analysis of the curves show a cardiac rate of 50 per minute; the rhythm is regular; complete heart block is present as is shown by the varying position of the P-waves in relation to the R-T complex. There is no disturbance of the muscle balance. Aside from the presence of block, there are no definite electrocardiographic indications of myocardial degeneration" (Fig. 105).

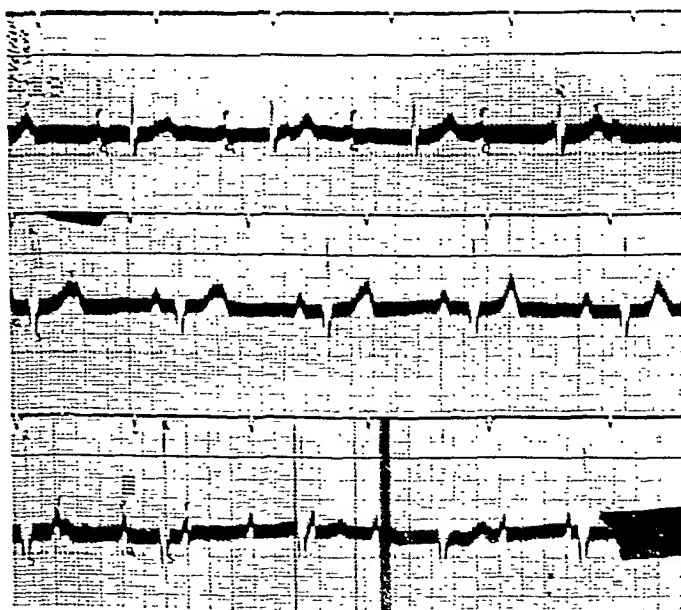


Fig. 105.

At present this child, who feels perfectly well, refuses to return for further examination because he fears that his activities will be restricted. His parents insist that they have no control over him. His activities which he does not restrict in any way do not seem to embarrass him.

The susceptibility of children with congenital heart defects is commented upon in many text-books. But are they any more susceptible, and if so, do they really succumb so readily as one is

children sent to "summer camps." Especially in the northeast and along the Delaware River Canal camps this condition is frequent, due to the dampness and lack of proper precautions particularly with reference to exposure following swimming and wearing damp clothing, night or day.

The promise of immunity or prevention of relapse following tonsillectomy and adenoidectomy will cause embarrassment sooner or later. This procedure cannot remove the multitudinous sources of infection with them or prevent the invasion of the disease through the tissues of the throat sans lymphoid adnexa. Since recurrences or relapses occur from virus in the submiliary nodules it is foolhardy to assume that this possible portal of original entry still maintains the gateway to further illness alone. Surgery will never remove the foci of infection because of their constant location in vital tissues.

Long convalescence with carefully graded exercise, attention to hygiene, and guidance by the heart and pulse of each patient will necessitate more space in heart hospitals for potential heart damage cases. There can be no let down for the present at least in the same provision for heart salvage cases for the same graded care must be provided. Probably one slogan would cover their needs, "No fatigue or exposure!" Perhaps more attention could be given this particular problem if less time were spent on worn-out machines as is now practiced by the geriatrist with his heart problems in institutions caring for heart patients. This should make available bed space for early cases since here will be the answer to the question of how to lower the heart disease mortality rates.

The *anterior lobe of the pituitary body* is larger than the posterior lobe which it partially surrounds. Its structure is chiefly cellular. These cells are divided into two main groups, depending upon their ability to take stain, namely, (1) the chromophobes and (2) the chromophils. The chromophobes are epithelial cells whose granules cannot be stained by the usual laboratory methods. According to Rasmussen,² they constitute about 52 per cent of all the anterior pituitary body cells. The chromophils, on the other hand, are cells which stain readily with the usual laboratory dyes. These are further divided into two subgroups, depending upon the kind of dye by which they can be stained: (*a*) Acidophilic cells whose granules take only an acid stain such as eosin and acid fuchsin and are therefore also known as eosinophilic cells, constitute about 37 per cent of all the cellular elements of the anterior pituitary body, and (*b*) basophilic cells whose granules can be stained only with basic dyes constitute about 11 per cent of all the cells comprising the anterior pituitary body. The three groups of cells just mentioned, namely, the chromophobes, the acidophils and the basophils differ from each other not only in staining peculiarities, but also in function.

The basophilic cells seem to play an important rôle in sexual development. Cases of dystrophia adiposogenitalis (Fröhlich's syndrome) have been reported in which these cells have shown an atrophic change. Hyperfunction of the eosinophilic cells because of an adenoma is said to be responsible for acromegaly. The opinion is expressed by Biedl³ that the chromophobes are the mother cells from which acidophilic or basophilic cells may subsequently be differentiated. Therefore when affected they may interfere with both growth and sex development. It is also probable that the chromophobe cells secrete a specific hormone as yet unnamed. The last word has not as yet been said on this subject.

That the anterior pituitary body has at least two hormones was shown by the comprehensive experiments of Evans and Long⁴ in 1921-1922, and in 1928 by Evans and Simpson⁵ who elaborated a hormone extractible in an alkaline medium which

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FIVE TYPES OF HYPOPITUITARY ENDOCRINOPATHIES

WE shall here devote our attention to a number of cases that were formerly termed "freaks," but are now more charitably designated as "endocrinopathies."

The intensive study of the endocrines during the past decade has considerably clarified our understanding of the part played by the ductless glands in certain anomalies. While much still remains to be explained as to the etiology of many of the endocrinopathies, there exists a working knowledge which is fairly adequate for the management and treatment of certain of the diseases of the ductless glands.

The Pituitary Gland.—The pituitary gland is possibly the most important of the ductless glands because of the wide range of influence it seems to exert both before birth and during the various ages after birth.

The pituitary gland is a composite of four distinct structures: (1) The anterior pituitary body, (2) the posterior pituitary body, (3) the pars intermedia, (4) the pars tuberalis.

The pituitary body, because of its position in the sella turcica, is usually of a definite size, weighing about 0.6 Gm., although under certain circumstances it may fluctuate within narrow limits. Thus we find that it is larger in the female than in the male, and that it is somewhat larger during menstruation than in the interim. During pregnancy it becomes considerably enlarged and Erdheim¹ has shown that the pituitary body is larger in the primipara than in the nullipara, and larger still in the multipara than in the primipara. After gestation the pituitary body recedes somewhat but not to its pregestation size.

of cells into the posterior body, a condition never found normally in that lobe. This may be explained only on the basis that having cut off the escape of the secretion along the stalk, it must of necessity invade the posterior lobe.

The *pars tuberalis* consists of numerous vesicles lined by basophilic cells. Its function is not entirely clear; it is, however, quite possible that the stalk is the connecting link between the hypothalamus and the pituitary body and permits exchange of impulses between the two and, also, that it may have functions which to some degree are ascribed to both the pituitary body and the hypothalamus. Conditions such as cerebral obesity, diabetes insipidus, hibernation, etc., may possibly be due to some extent to malfunction of the *pars tuberalis*.

When normal, the pituitary gland elaborates a number of hormones of such quality and quantity as is required for the body's performance of certain functions. When abnormal, the gland's activity may be distorted so that its hormones are not secreted in proper quantities and are not of normal quality. The abnormal function may manifest itself in hypersecretion or hyposecretion of one or of several of its hormones, or in hyposecretion of some hormones and at the same time, hypersecretion of others. Such imbalance is responsible for the production of a great variety of endocrinopathies.

Hypopituitarism.—Hypopituitarism embraces all conditions resulting from a diminished output of one or more of the pituitary hormones. There are various types of hypopituitarisms, depending upon five factors:

1. Age; that is, at what period of the individual's life, during infancy, adolescence or adulthood, the pituitary hormones became scarce.

2. Degree of hypopituitarism; a moderate scarcity may cause mild symptoms and a pronounced scarcity will produce well-marked changes in the individual.

3. Specific hormone affected; that is, growth, sex or other hormones.

4. Accompanying disfunction of other endocrine glands such as the thyroid, the suprarenals, etc.

has a specific influence upon growth. This hormone is now known as "the pituitary growth hormone." They also extracted another anterior pituitary hormone in an acid medium and found that it stimulated the gonads, thyroid and adrenal cortex. This is now known as the "pituitary sex hormone." An excess of pituitary sex hormone often counterbalances the growth hormone and may cause an arrest in body growth. Thus, in children the growth hormone is active and the sex hormone is dormant. The reverse is true in adults. At times hypopituitarism may cause an arrest in both sex and growth hormones, giving rise to both sexual and somatic infantilism. According to Aschheim and Zondek⁶ there are two sex hormones: prolan A, controlling ovulation, a follicle-ripening hormone, and prolan B, a luteinizing hormone which influences luteinization. This is doubted by more recent experimenters who believe that there exists only one anterior pituitary sex hormone. When it is secreted in small amounts it stimulates ovulation and in larger quantities it further stimulates the ovary to luteinization.

The *posterior pituitary body* is composed chiefly of neuroglia cells and seems to be responsible for several hormones. Kamm⁷ and his co-workers obtained two substances: (1) A blood-pressure-raising substance now known as pitressin or surgical pituitrin, and (2) a uterine contracting hormone known as pitocin or obstetrical pituitrin. It is also believed by some observers that the posterior pituitary body exerts an influence upon fat metabolism, carbohydrate metabolism and water metabolism. Others, however, believe that the latter functions are influenced by the anterior pituitary body or the hypothalamus.

The *pars intermedia* is a thin, poorly vascularized structure formed of densely packed basophilic cells and lying between the anterior and the posterior lobes. Many authorities believe that the posterior lobe hormones are actually secreted by the *pars intermedia* cells and are stored in the posterior lobe whence they may be extracted. Cushing and Goetsch⁸ have shown that clipping the stalk of the pituitary gland without interfering with its blood supply causes an accumulation of a large number

growing soon after the last two illnesses. She attended school up to the sixth grade, but voluntarily stopped at the age of twelve because the other school children teased her and called her infant. The breasts began to enlarge when she was eighteen years old; she has never menstruated and seems to be asexual. She was always indifferent to boys and had no more emotional reaction to boys than to girls.

The physical examination reveals her as a well-developed somewhat slender child, 44 inches in height, weighing 45 pounds. The breasts are somewhat prominent and the hips are comparatively large; the abdomen also shows some prominence and has a fair amount of adipose tissue. The head is normal in proportion to the body and is covered with a luxuriant growth of thin glossy hair; the forehead is fairly high; the eyes are bright; the nose is small; the lips are of normal appearance and she has a tendency to pout. The face is rounded. The skin over the entire body is soft and delicate. The arms and legs are slender, though one may notice enlarged veins at the dorsum of her hands and feet. She gives the general impression of being a well-nourished child or seven or eight years of age, or rather she presents the appearance of an adult viewed through the large ends of a pair of opera glasses. Her mentality is that of an average child of twelve years. She talks and sings in a high-pitched childish voice and performs a rather intricate act of dancing and repartee on the stage in the company of a group of other dwarfs.

Comment.—The interesting features in this case are: (1) The family history reveals endocrinopathies such as Graves' disease in a maternal uncle, and polydactylism in a younger brother. (2) At birth and several years thereafter she was normal mentally and physically, though delicate. (3) Her somatic development was interrupted at an early age possibly by parotitis and otitis media. (4) The pituitary defect occurred before the age of secondary sex differentiation, therefore she had not developed sexually and practically remained a young child throughout life.

The etiologic factors here responsible for this condition may be assumed as being an acute suppurative disease in one who has a familial endocrinopathic predisposition. The pathology may be inferred from her symptoms; it is therefore assumed that this patient is an example of hypopituitarism of the anterior lobe of the pituitary body in which both the eosinophilic and basophilic cells have either entirely or almost entirely, ceased functioning at an early age.

Treatment.—In this case treatment is practically useless as she has long passed the period in which potential function

5. Amount of neighborhood pressure symptoms exhibited, when due to tumor of the pituitary body.

**INFANTILISM, SOMATIC AND SEXUAL WITHOUT ADIPOSITY
(LORAIN-LEVY TYPE OF HYPOPHYSEAL INFANTILISM)**

This type of endocrinopathy is well illustrated by Miss A. L., aged twenty-eight.

She is one of four children, two older and one younger than herself; the other siblings are of normal stature. Her mother is rather stout, weighing over 200 pounds. She has one uncle who has exophthalmic goiter and her younger brother has six fingers on each hand.

The patient at birth weighed 6 pounds, 4 ounces but appeared normal in other respects. Her delivery was spontaneous and at full term. She was breast



Fig. 106.—Infantilism, somatic and sexual without adiposity (Lorain-Levy type of hypophyseal infantilism). Miss A. L., aged twenty-eight; height, 4 feet, 4 inches; weight, 48 pounds.

fed until one year of age. The first tooth, lower central incisor, appeared at eight months; dentition generally was somewhat delayed. She began to walk at the age of a year and a half, and to talk earlier than that. She was a fairly normal child but more delicate than her brother and sister. She had measles followed by bronchopneumonia at one year of age, diphtheria at three, diphtheritic croup at three and one half, and mumps and otitis media at the age of four years. The mother states she had noticed that the patient stopped

school until his fourteenth year. He is quite intelligent, is a fluent talker and is keenly interested in daily topics. He speaks in a high-pitched voice which reaches the falsetto when he becomes excited.

Physical Examination.—He is 4 feet, 8 inches in height, has a luxuriant growth of hair on his head, but has never found it necessary to shave his face (though he is a barber). His forehead is high, the eyes have a mongoloid slant, the face is round, the nose is small and the lips are thin and soft. The neck shows no enlargement, the supraclavicular spaces are depressed. The mammary glands are large and pendulous, resembling those of a mature woman; the hips are large; the abdomen is obese and hangs downward; the thighs are large and the ankles and wrists are small. The pubic hairs are scant and of the female type of distribution, the base of the triangle pointing upward. The genitals are not visible when he is in the standing posture. In the dorsosacral position, the relative size of his breasts is more noticeable as is also the sparsity of the pubic hair. The penis is small and there is a total absence of a scrotum. Needless to say he is unmarried, although he states that he likes ladies' company.

Comment.—The syndrome presented by this patient is most likely of anterior pituitary and gonad origin. His pituitary growth hormone probably stopped functioning at the age of puberty, as his height is that of a boy of thirteen years. Normally, the pituitary sex hormone becomes active at or about puberty when it begins to stimulate the gonads. This has apparently not occurred in this patient. His testes are not palpable but since he has many male characteristics, we infer that his testes are intra-abdominal (cryptorchism), and possibly rudimentary. The female type of breasts and pubic hair distribution, the high-pitched voice, the absence of hair on his face, and, I may add also, his effeminate mannerism, indicate a eunuchoid state of hypopituitarism.

Treatment.—It may be advisable in this case to explore his abdomen surgically so as to determine the presence of testes. The release of testicular compression, if not too late, may be of some value. Implantation of simian or human testicles in a patient of this type is worth trying. It can do no harm and it may satisfy his and our curiosity.

HYPOPITUITARISM (DYSTROPHIA ADIPOSEGENITALIS)

Miss E. S., aged twenty-seven, represents another type of hypopituitarism in which the growth hormone is unaffected, but the sex hormone of the anterior pituitary body is definitely deficient. This young woman was perfectly normal at birth and, until her thirteenth year, presented no abnormalities. Menstruation

can be awakened. To attain any measure of success in the treatment of childhood endocrinopathies, it must be begun as soon as diagnosed and before the age of puberty. In this case, stimulation by sex and growth hormone administered hypodermically or by mouth, or stimulation of the pituitary gland by x-ray would probably be of no avail. Even if treatment along the line just mentioned could to some extent stimulate somatic and sexual development, I would be inclined to oppose it for psychological reasons. Why transform a happy child into an unhappy and maladjusted adolescent!

HYPOPITUITARISM WITH CRYPTORCHISM (PSEUDOHERMAPHRODISM)

Mr. T. C., aged thirty-four, referred to me by Dr. H. Orloff, is an example of another type of hypopituitarism associated with arrested and possibly perverted sexual development.

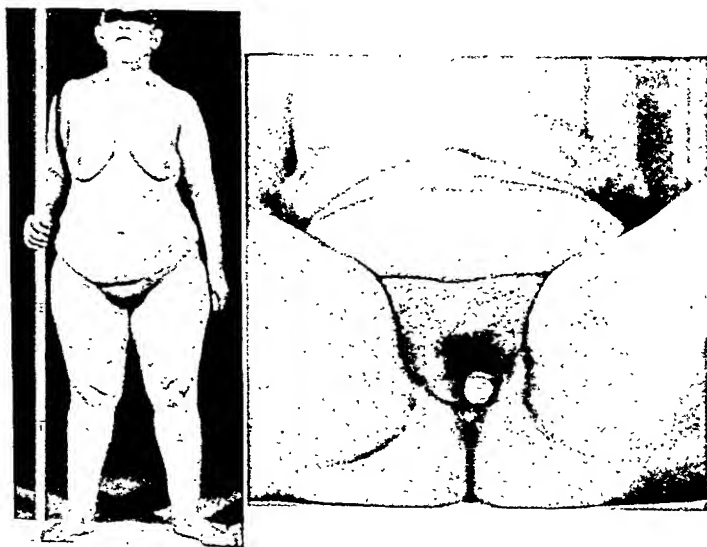


Fig. 107.—Hypopituitarism with cryptorchism. Mr. T. C., aged thirty-four; height, 56 inches.

This patient is one of a family of ten. His father and mother and the other nine children are all well and present no endocrine anomaly. He does not remember much about his youth, but believes that he has always been well. He came to this country from Italy at the age of eight years, and attended

Previous Medical History.—She had the usual childhood diseases during early childhood, and typhoid fever when she was not quite thirteen years of age. Her first menstruation appeared about one month after her convalescence from typhoid fever.

Her chief complaint, when first seen, was weakness, fatigability on least exertion, frequent headaches, irregular menstruation and obesity. The appetite was fairly good and she stated that notwithstanding the fact that she eats less than any member of her family, she steadily gains weight. Her basal metabolic rate varied between minus 3 and minus 11, and was most often minus 8. The visual fields were normal. The x-ray examination of the sella did not show any definite abnormality.

Comment.—This patient presents what is generally recognized as the pituitary type of obesity. The basophilic cells and probably the chromophobes of the anterior pituitary body are at fault, since the sex hormone is definitely inefficient. The eosinophilic cells responsible for the growth hormone were either too active because of pituitary disease or were compensating as a result of basophilic hypo-activity.

Treatment.—The treatment of this type of obesity associated with gonad hypo-activity consists of: (1) An attempt at reduction of the obesity, and (2) the reestablishment of normal ovarian function. Occasionally the correction of one may result in renewed activity of the other. It is, however, advisable to attack both problems simultaneously as they have a common cause. The treatment is to be carried out along a more or less definite plan, as follows: (a) Hygiene, (b) diet, (c) medication and x-ray applications.

(a) *Hygiene.*—In the absence of myocardial, renal and pulmonary disease, the patient is advised to take a daily cold shower or bath, and a sweat bath twice a week. Physical exercise, to a point where it causes profuse perspiration, will help to increase muscle tone and aid to some extent in the dehydration process. Fresh air and sunshine should be indulged in as much as the individual's time will permit.

(b) *Diet.*—An important step in the treatment of obesity, as pointed out by Wohl,⁹ is dehydration by diet and medication. A fat and carbohydrate poor basal maintenance diet, containing a minimum quantity of sodium chloride should be formulated for each individual under treatment. It is often advisable to

began at the age of thirteen years. The first flow was profuse, lasted for two weeks, and she was obliged to remain in bed because of the menorrhœa. The second menstrual period arrived three months later. It was scanty in amount, lasting only two days, and she only partially soiled two napkins with greenish-brown stains. She then remained amenorrhœic for a year. Since then until a year ago when she came under treatment, her menstruation was irregular as to time and quantity. The time interval was from two weeks to four or five months, and the quantities varied from a few stains to a large amount. The flow lasted anywhere from several hours to eight days or longer. After her first

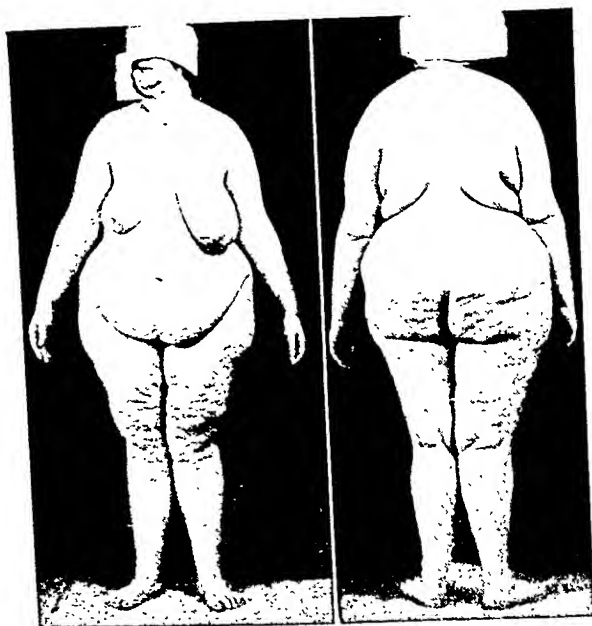


Fig. 108.—*Dystrophia adiposogenitalis*. Miss E. S., aged twenty-six; weight, 300 pounds; height, 5 feet, 6 inches.

menstrual period, she began to gain in weight; at the age of thirteen, she weighed 94 pounds, and measured 5 feet; at the age of fifteen, she weighed 195 pounds and measured 5 feet, 4 inches; at the age of twenty-six, she weighed 300 pounds and measured 5 feet, 6 inches. She was exceedingly fat, the greatest bulk was noticeable around the hips, abdomen, buttocks and thighs. Her facial features were regular and pretty, except for a fairly luxuriant growth of hair upon her upper lip and chin. A depilatory had to be used once a week. Her forearms, wrists, legs and ankles were unusually small in comparison to her body. Her family history is entirely negative as to endocrinopathies. Her father and mother are both rather obese. The father weighs 170 pounds and is 5 feet, 4 inches tall, and the mother weighs 220 pounds and is 5 feet, 6 inches tall. Her two brothers are of normal proportions.

will raise the basal metabolic rate in an athyroid patient approximately 2.5 per cent and maintain that level for about two weeks. The basal metabolic rate is to be raised in this instance from minus 8 to plus 10, that is 18 per cent. This may be accomplished in an athyroid patient by giving one injection of about 7 mg. of thyroxin intravenously, but in a case like this where the thyroid gland is not entirely inactive, about half that dose or 3.5 mg. would be sufficient. The full physiologic effect of thyroxin is not obtained until the tenth to the fourteenth day after its administration. Therefore two weeks after the initial dose of thyroxin $\frac{1}{2}$ to 1 grain of desiccated thyroid gland should be given daily by mouth so as to take care of the daily bodily requirement. Desiccated thyroid gland may be used without the preliminary injection of thyroxin. According to Englebach,¹¹ 1 grain of desiccated thyroid gland given by mouth will raise the metabolic rate approximately 5 per cent; therefore the daily oral administration of $3\frac{1}{2}$ to 4 grains of desiccated thyroid gland in three divided doses will keep the metabolic rate of such a patient at the desired level. If untoward nervous symptoms appear, the basal metabolic rate should be investigated and if found too high, the dosage of thyroid medication should be decreased or temporarily discontinued.

Pituitary activity may be stimulated by the daily or bidaily intramuscular injection of 1 cc. of antuitrin S (prolan B), or pituitary sex hormone. Zondek¹² reported favorable results in several cases of pituitary amenorrhea by the administration of six to nine injections of 60 rat units each, every month for several months. It is also desirable to increase the vascularity of the uterus. This may be accomplished by the daily oral or hypodermic administration of 100 rat units of some form of follicular hormone such as oestrin, theelin, estrogen, theelol, etc. This form of medication is to be administered after the method of Zondek, Mazer and others in monthly courses over a period of time sufficiently long to obtain either the desired beneficial results or to determine that it is useless for the case in question. It is usually advisable to supplement the hormonal treatment with x-ray treatment. When the hormonal

further decrease that diet by 10 to 15 per cent below their basal requirements. Should the patient lose weight too rapidly under this régime, excessive weakness because of too rapid emaciation may be avoided by arranging the diet so that the patient will lose 2 pounds in one week and then regain 1 pound the next week. This alternate greater loss and lesser regain in a step-ladder fashion or "lysis" I find causes the patient little inconvenience and often avoids fatigue. The daily fluid intake should be restricted to about 1000 cc. The bowels should be kept loose with the aid of a saline, such as phosphate of soda or Epsom salt, which is to be taken in concentrated solution preferably in the morning on arising. Spices, salt, condiments and alcoholic beverages are to be restricted.

(c) *Medication*.—Dehydration may further be accomplished by stimulating the kidneys with occasional doses of theocin, given in 5-grain doses twice daily for three days out of every ten, and by the intravenous administration of 0.5 to 1 cc. of salyrgon or the intramuscular injection of 1 cc. of novasurol. While dehydration is probably the best means by which a substantial reduction in weight may be accomplished in the obese, care must be taken in the administration of the mercurials as some patients have an idiosyncrasy to them and may develop stomatitis, enteritis, or renal congestion. In the presence of nephritis, novasurol and salyrgon are to be avoided and theocin should be used sparingly if at all.

Hormonal Treatment.—To reestablish normal menstrual periodicity it is necessary to fulfill three indications: (1) To increase general cellular activity by increasing the basal metabolic rate, (2) to stimulate the incrtion of pituitary sex hormone and (3) to stimulate ovarian function.

When the basal metabolism is a low normal, as in this patient, minus 8, in order to increase general cellular activity, it would be well to convert the low normal to a fairly high normal, if possible to plus 10. To accomplish this, desiccated thyroid gland may be given by mouth or thyroxin may be administered intravenously in doses sufficient to obtain the desired effect. According to Plumber and Boothby¹⁰ 1 mg. of thyroxin

after her last cesarean section a panhysterectomy was performed because of a uterine tumor. The wound has never healed. Since her operation she had gained 75 additional pounds.

Physical Examination.—She is an extremely fat white woman, measuring 4 feet, 9 inches in height and weighing over 400 pounds. The head is normal in size and contour and is covered with a luxuriant growth of dark hair. The eyes are normal; there are no visual defects and the visual fields are normal. The hearing is normal, and there are no ear defects. The nose is small and presents no abnormalities. The mouth, the lips, the tongue and the throat are normal; she has a few carious teeth. The skin is generally smooth and normally moist. The chest is of normal contour, though she has large pendulous breasts. The



Fig. 109.—Cerebral obesity. Mrs. L. K., aged thirty-two; weight, over 400 pounds; height, 4 feet, 9 inches. (Dr. Weisenberg's service, Philadelphia General Hospital.)

heart and lungs are normal. The abdomen is of immense size, almost reaching her knees when she stands upright. The abdominal wall is covered with a huge layer of fat. In contrast with the general obesity, her ankles and wrists are unusually small. Neurological examination reveals no sensory or motor defects. The patient is intelligent, cooperative, pleasant and happy. The blood count shows a slight secondary anemia. The blood chemistry shows urea nitrogen 14 mg. per 100 cc. of blood; glucose, 90 mg. per 100 cc. of blood. Other constituents such as calcium, phosphorus and cholesterol are also normal. The basal metabolic rate is minus 8. x -Ray examination of the head reveals the following: The sella is smaller than normal, the floor is thin, but it is intact; the anterior and posterior clinoids are normal.

treatment cannot be indulged in because of expense, the x-ray treatment alone may be used. Five or six x-ray exposures simultaneously to the ovaries and pituitary region constitute a course of treatment which is spread out over a period of six weeks. One treatment per week is usually sufficient. If the results are inadequate, Mazer¹³ advises that after the lapse of two months, a second and if required a third course of treatment should be given. The results are at times surprisingly good, though there are many such cases which fail to respond.

Under this type of treatment this patient has lost 120 pounds in one year, and she now menstruates with regular periodicity. Hormonic treatment was discontinued after the fifth month. However, she is still on a restricted diet.

CEREBRAL OBESITY

Obesity of cerebral origin is fairly common; at times it may be associated with definite pituitary and gonad dysfunction as represented by E. S. (Fig. 108), and at other times no definite or only mild pituitary or gonad hypofunction is manifested. Mrs. L. K. is a good example of this last type. It is quite possible that in such instances the hypothalamus or other structures in the pituitary area may be at fault.

Mrs. L. K., was admitted to Dr. Theodore Weisenberg's service in the Philadelphia General Hospital on 7/16/22. Her chief complaint was epigastric pain some time after taking food, dyspnea, frequent headaches and a voracious appetite. She is one of eight children; her three brothers and four sisters are normal and present no endocrinopathies. Her father is of normal stature and is not obese. Her mother weighed 170 pounds. The patient was born prematurely, weighed only 3 pounds at birth and was delicate until her fourteenth year. She had measles, chickenpox, mumps and pneumonia during childhood. Between her fourteenth and fifteenth years she gained weight rapidly so that, at the age of fifteen years, she weighed 187 pounds. Menstruation began at sixteen years of age; it was irregular and scanty and soon after her first menstrual period she began to lose weight. At the age of eighteen she weighed 135 pounds. She was married at the age of nineteen years; her weight then was 139 pounds. Her first child was born nine months later. After the birth of her first baby she started to gain in weight so that at the age of twenty-one years she weighed 180 pounds. At twenty-three years, after the birth of her second child, she weighed 260 pounds. Fourteen months later, after the birth of her third child, she weighed 300 pounds. Her fourth and fifth babies were delivered by cesarean section. After the birth of her fifth child she weighed 388 pounds. Three weeks

M. F. was admitted to the Philadelphia General Hospital on the service of Dr. J. W. McConnell with the diagnosis of adiposis dolorosa, chronic myocardial degeneration and epilepsy. She remembers little about her early childhood. At the age of eight years, secondary sex characteristics (pubic and axillary hair and breast development) appeared. Shortly after that she began to gain in weight, and at the age of nine, she had her first menstruation. It appeared regularly every twenty-eight days. The flow was profuse, lasting four days. At sixteen years of age she was fully grown. She had two pregnancies, at eighteen and at twenty-one years of age respectively. She had an appendectomy and salpingo-oophorectomy at the age of twenty-six years. Her father and mother were

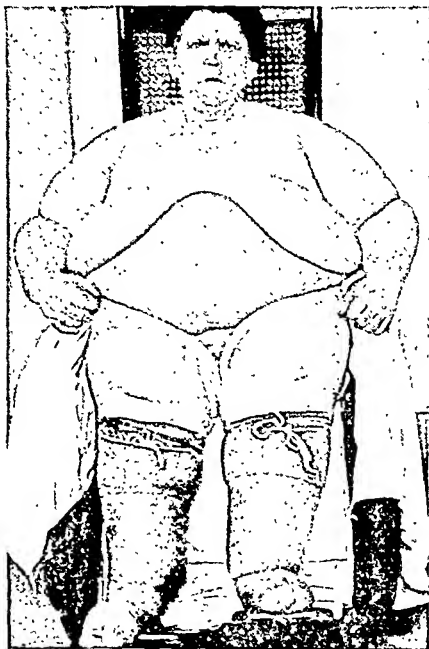


Fig. 110.—Adiposis dolorosa. M. F., weight, 380 pounds. (Dr. McConnell's service, Philadelphia General Hospital.)

both stout. She knows little about her family except that some of her people had diabetes. The first attack of epilepsy occurred at the age of thirty-three years. It was preceded by a severe frontal headache. She has since had many attacks which come on at irregular intervals and are preceded by headaches. Her appetite is very good; she is particularly fond of candy and sweets. She has no digestive disturbance except when she overeats.

Examination.—The patient is excessively stout, weighing 380 pounds. She has a quarrelsome disposition and is excitable. The skin is smooth though somewhat dry, and she has several patches or psoriasis on both elbows. The breasts are large, the abdomen and upper and lower extremities are bulky. Palpation of

Comment.—This patient presents a number of striking and unusual features.

She was a premature baby weighing 3 pounds at birth, and was underdeveloped until her fourteenth year. At the usual age of puberty, though not menstruating, she gained weight rapidly until her sixteenth year when she first menstruated. After her first menstruation she gradually began to lose weight; her menstruations were scanty and irregular. Notwithstanding her oligomenorrhea, she gave birth to her first child nine months after marriage and gave birth to five children in rapid succession; further childbearing was prevented only by hysterectomy. After each childbirth as well as after her hysterectomy, she gained rapidly in weight. At the age of nineteen years she weighed 139 pounds and at the age of thirty-two years, she weighed over 400 pounds, so that in thirteen years she had gained over 260 pounds. There appears to be some evidence here of pituitary hypofunction as is indicated by her delayed first menstrual period and by the oligomenorrhagia. This, however, has not interfered with her fertility. The smooth skin and unusually small wrists and ankles also incriminate the pituitary gland. Since her "pituitary signs" are so vague it is assumed that the origin of this patient's obesity is probably in the hypothalamus, and the pituitary gland because of its proximity to the hypothalamus, participated in some measure in this dyscrasia.

Treatment.—The treatment should here be directed to her obesity and should consist of a salt-poor basal maintenance diet and moderate dehydration.

ADIPOSIS DOLOROSA (DERCUM'S DISEASE)

Adiposis dolorosa was first described by Francis X. Dercum in 1888. Its etiology is still a matter of dispute. Some observers believe that the pituitary body is responsible for this condition. Others are of the opinion that it is a pluroglandular affection in which the thyroid plays an important rôle, and still others question its endocrine origin. This case seems to indicate that the pituitary body might be an etiologic factor.

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any part of her body causes her to complain of pain. This is particularly noted where the fat is thickest over the back of her neck, the arms, the abdomen, and the thighs. Her heart shows definite evidence of myocarditis; her blood pressure is 115/76. Her lungs are normal. The size of the liver and spleen cannot be determined by physical examination because of her obesity. The blood examination shows normal findings. The urine shows a trace of albumin. x-Ray examination of the sella turcica shows that the sella is larger and shallower than normal and that there is a bony outgrowth extending into the sella from the under surface of the anterior clinoid process. The ophthalmological examination reveals contracted visual fields.

Comment.—The outstanding features in this case are early maturity, the development of epilepsy at the age of thirty-three years, the profound general obesity, the tender areas over the body, the ungovernable temper and signs of intracranial pressure, with positive x-ray findings in the pituitary region.

Diagnosis.—Notwithstanding the fact that her arms and legs are stouter than is the rule in such cases, and that she showed precocious sexual development at a very early age, there is sufficient evidence to warrant a diagnosis of adiposis dolorosa. The great adiposity, the many tender and painful areas, her ungovernable temper, verging on psychosis, and the intracranial pressure, as indicated by the x-ray examination and manifested by her severe frontal headaches, the contraction of the visual fields, and the development of epilepsy in adulthood all warrant the classification of this patient as a case of adiposis dolorosa or Dercum's disease.

In conclusion I wish to emphasize that there exists a great number of pituitary endocrinopathies; some are recognizable as distinct entities, others are shrouded in ambiguity and still others are so vague as to be entirely overlooked. The 5 cases here exhibited are intended to serve as examples of certain types of pituitary malfunction and represent only a small number of the existing types of pituitary endocrinopathies.

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arteries; (2) extensive destruction of the media, including the elastica interna or the entire wall of the vessel, with aneurysmal dilatation and thrombosis, and subsequent complete organization; (3) a periarterial healed granulation tissue mantle, consisting of dense fibrous connective tissue with capillaries and deposits of hemosiderin; (4) extensive destruction and even aneurysms in arteries with marked proliferation of the intima; (5) healed infarct scars of most organs, and (6) marked stenosis of both coronary arteries with destruction of their walls. Kountz also calls attention to the great similarity in the afferent glomerular vessels in the cases of periarteritis nodosa, and the lesions described by Fahr as a type of malignant hypertension.

With these facts in view we wish to record again a case of periarteritis nodosa which has been under our care for the past year.

History.—A white man, P. McE., aged twenty-seven, was first seen at the Philadelphia General Hospital on June 13, 1932. He complained chiefly of inability to walk, of one week's duration, together with pain in the side of the neck, behind the shoulders, in the right arm, dorsal surfaces of the feet and the calves of the legs. For the last five years the patient had averaged weekly drinking of 3 pints of alcohol. Following an alcoholic debauch two months before admission he noticed for the first time a soreness and tenderness over the left side of the chest, the skin over both shoulder blades and on the forehead just above the left eye. Three weeks before admission he developed a dull aching sensation in the calves of the legs which was increased in severity while walking. Finally he was forced to bed seven days before admission. During this time he developed a dull deep-seated pain in the right side of the neck, a superficial tenderness over the dorsum of the feet and a soreness throughout the biceps of the right arm. The sore spots on the back of the shoulders and the side of the chest became worse while the spot above the left eye became larger and changed to a purplish color. His appetite has been good and he has lost no weight. He has no symptoms referable to the heart, lungs, gastro-intestinal tract or genitourinary system. Past illnesses, whooping cough and chickenpox, influenza (1918). No venereal history. Family history negative. Occupation, roofer.

Physical Examination.—On admission, revealed a fairly well-nourished individual, lying in bed almost motionless because of the severe pain which was produced when pressure was exerted over different areas of the body. Pain was not present in the joints but seemed limited to the skin and muscles. His skin was moist and he seemed somewhat nervous and apprehensive. His blood pressure was 140/100, pulse rate 112, temperature and respirations were 100.5 F. and 25 respectively. There appeared on his forehead just above his left eye

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PHILADELPHIA GENERAL HOSPITAL

PERIARTERITIS NODOSA

PERIARTERITIS nodosa is a specific infectious disease probably caused by filtrable virus, with elective affinity for the arteries. The organs usually involved are the kidneys, heart, liver, muscles, peripheral nerves and gastro-intestinal tract. Any or all may be affected. It was first described by Kussmaul and Maier in 1866. In 1925 Gruber collected from literature 114 cases and discussed them at length. He explains that the great difficulty in clinical diagnosis is due to the variability of the disease picture, most of these diagnoses being made post-mortem. The characteristic picture is one of sepsis with scattered local manifestations of vascular disease which baffle explanation, and anatomically, it is characterized by nodular inflammatory foci in the walls of the smallest or middle-sized arteries.

The symptoms are septic temperature, polyneuritis and polymyositis, hematuria or nephritis, abdominal cramplike pains, and progressive emaciation. There is great variability of symptoms, and a tendency toward acute exacerbations suggestive of periarteritis nodosa. In addition to these symptoms Kountz adds jaundice as a characteristic finding. This he ascribes to widespread changes in the blood vessels of the liver and the gallbladder. Arkin, in a very careful study of 5 cases, divides the pathologic changes into three stages: (1) Alterative-degenerative, (2) acute inflammatory, and (3) granulation tissue. The characteristic histologic changes found were: (1) Proliferation of the intima with new formation of elastic fibrils, leading to stenosis of even complete occlusion of the

Laboratory Examination.—June 16th, 5,000,000 red blood cells, 10,000 white blood cells, with hemoglobin 90 per cent, polymorphonuclears 71 per cent, lymphocytes 27 per cent and monocytes 2 per cent. A clotting time of two and one-half minutes and 110,000 platelets. The blood sugar was 92 mg. and urea

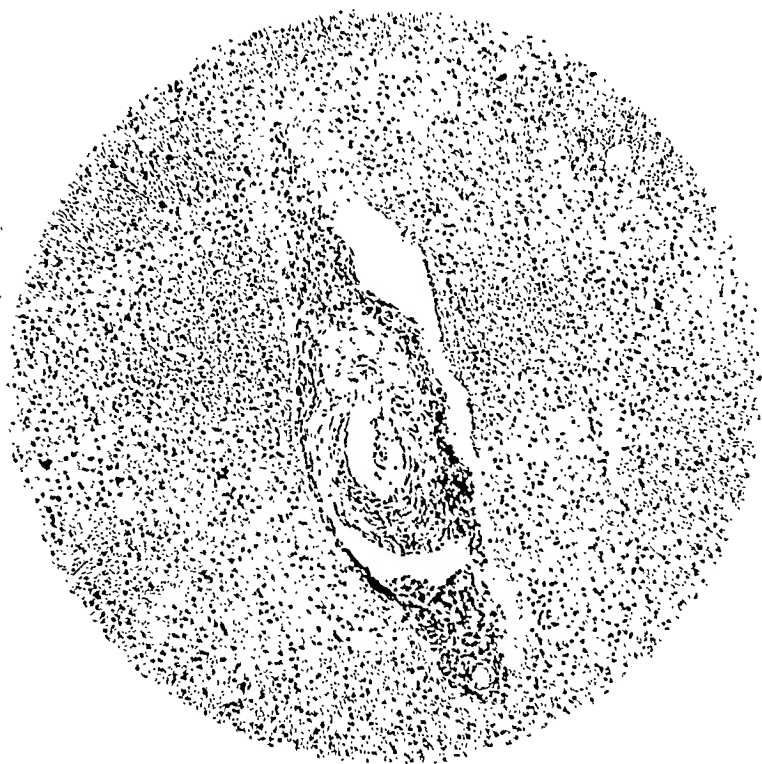


Fig. 113.—The small arterioles are entirely or in part surrounded by a sub-acute cellular exudate, composed of histiocytes, plasma cells, polymorphonuclears and lymphocytes. The media is in some places infiltrated by a similar exudate and in other spots has undergone partial necrosis, quite similar to that seen in the afferent capillaries of the glomeruli in malignant arteriole nephrosclerosis of Volhard and Fahr. The subintimal space is edematous. Endothelial lining is swollen and in parts the endothelial cells have disappeared, only shadows remaining. The capillary lumen is narrowed and almost occluded, the walls almost touching.

11 mg. Total protein 5.98 per cent and chlorides 722 mg. Blood Wassermann and Kahn were negative. Spinal fluid was negative. Urine was brown in color, acid in reaction, 1.030 specific gravity, and was negative for albumin and sugar. A few epithelial cells and leukocytes were seen. June 30th, an x -ray of the heart, lungs, skull and long bones was negative. Eyegrounds were negative.

a purplish, tender indurated lesion 3 x 2 cm. in diameter and well above the level of the skin. Eyes negative except for frequent winking of the lids. The tongue was coated, the lower teeth carious and the upper ones false. Tonsils were medium sized and cryptic, but not acutely inflamed. Pharynx was injected. The neck showed a few enlarged, slightly tender lymph nodes on the right side. An irregular tender nodule about the size of a small pea was felt in the right sternocleidomastoideus muscle. The chest showed three skin lesions; one behind each shoulder blade and the other one on the left side of the chest in the mid-axillary region. Each lesion was about the size of the palm of the hand and was well raised above the level of the skin margin. They were purplish in color, very



Fig. 111.



Fig. 112.

Fig. 111.—Picture of both forearms showing distinct nodular deformities which were very painful, with diffuse hemorrhagic areas.

Fig. 112.—Nodular eruptions with ecchymoses scattered over the back.

tender and felt nodular throughout. The heart and lungs were normal. Abdomen was negative. The prostate was normal. The extended fingers of both hands showed a slight tremor. Both upper and lower extremities showed muscular weakness but this was more marked in the right extremity. A hyperalgesia was present over the extremities but more noticeable over the lower extremities. The calves of the legs were exquisitely tender to pressure. The knee jerks appeared normal or slightly hyperactive as well as the biceps and triceps reflexes. The axillary and epitrochlear lymph nodes were enlarged but not tender.

A diagnosis was made of alcoholic multiple neuritis, and a possible hemorrhagic purpura.

of the autogenous vaccine was given intravenously. The dose was gradually increased to four hundred million, and this was given at weekly intervals until the patient was discharged from the hospital on December 24, 1932. He was readmitted on January 3, 1933, because of weakness and fever. Again his temperature became lower, he regained strength, and was discharged from the hospital on March 7, 1933.

Patient was treated with nonspecific immuno blood transfusions, typhoid and autogenous vaccines. Carious teeth were extracted and all sources of foci were sought for during his stay in the hospital. Following these treatments he would appear better and the skin manifestations were less obvious; but soon new crops would appear again and the temperature would vary from normal to 102 F. On the day he was discharged the nodules appeared larger in size and more extensive, but less tender. The fingers of both hands could not be fully extended.

Approximately one year after patient was first seen, he is still able to be about. The acute exacerbations have gradually tended to diminish in frequency and severity. He still continues to lose weight, and remains quite prostrated.

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Basal metabolic rate was plus 25. Sputum was negative for tubercle bacillus. Icterus index was 6 and van den Bergh was negative. The phenolsulphonephthal-ein elimination was 20 per cent and 28 per cent. June 21st, the purplish skin lesions began to disappear and showed less tenderness than formerly. The right sternocleidomastoideus muscle was markedly tender and presented numerous nodules along its entire length. A blood count again today showed 4,000,000 red blood cells, 20,000 white blood cells, with 94 per cent polymorphonuclears, 4 per cent lymphocytes, 1 per cent monocytes, and 1 per cent eosinophils. His temperature ranged daily from 98.5 to 101 F. June 24th, several nodules were noticed in the soft tissues about the right knee joint and numerous ones were studded throughout the soft tissues of the right arm and forearm. These nodules were very tender, irregular in size, and appeared to be slightly red. There also appeared for the first time a partial paralysis of the ring and middle fingers of the right hand. The white blood cell count reached its highest on June 28th, with 22,000 containing 76 per cent polymorphonuclears. A biopsy of one of the nodules was taken from the subcutaneous tissue. During the same day a nonspecific immuno blood transfusion of 250 cc. was given. Thirteen hours following this transfusion the patient was clinically better. Most of the superficial tenderness had disappeared and the white blood cell count dropped to 12,000, and the temperature was at a lower level. Another similar transfusion was given the following day. June 30th, the biopsy report gave a pathologic diagnosis of periarteritis nodosa. Blood pressure was 130/78. A red area about 1 cm. in diameter appeared on the abdomen near the umbilicus. This was not tender.

On July 2nd the blood pressure was 120/80. The skin area on the forehead had increased to the size that it was on admission. Several tender nodules were studded throughout the biceps muscle of both arms and gastrocnemius muscle of both legs. Both arms and legs ached all day. Three days later another nodule appeared on the nose near the inner canthus of the left eye. On July 6th and 7th a nonspecific immuno blood transfusion of 300 cc. was given daily. The following day the patient was clinically better. Pain was not produced on pressure over any part of the body above the knees. The nodules actually seemed less in number and the partial paralysis of the fingers of the right hand had disappeared. However, the calves of the legs and the bottom of the feet remained tender. Crops of erythematous nodules have broken out on all parts of the body except the abdomen and disappeared at varying intervals. July 26th there reappeared a partial paralysis of the ring and middle fingers and included all fingers of the right hand. August 8th the patient presented similar skin lesions on the abdomen. These erythematous nodules were more extensive this day than ever before, and varied in size from a pinhead to the diameter of a dime. They involved the skin over the entire body except the scalp and the soles of the feet. Another biopsy was taken from the gastrocnemius muscle of the left leg, and the pathologic report again was periarteritis nodosa. Exactly one week after the lesion appeared on the abdomen the patient noticed that he could not extend the fingers of the left hand. The patient was allowed out of bed into a wheel-chair for the first time on August 8th. He continued being in the wheel-chair daily until September 24th, during which time he walked for the first time since onset of illness. September 26th a local tonsillectomy was done and a vaccine was made from the tonsils. On October 17th fifty million

of the autogenous vaccine was given intravenously. The dose was gradually increased to four hundred million, and this was given at weekly intervals until the patient was discharged from the hospital on December 24, 1932. He was readmitted on January 3, 1933, because of weakness and fever. Again his temperature became lower, he regained strength, and was discharged from the hospital on March 7, 1933.

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CLINIC OF DR. M. A. BURNS

FROM THE NEUROLOGICAL SERVICE OF THE
JEFFERSON HOSPITAL

MULTIPLE SCLEROSIS

IN recent years various authors have written more or less extensively concerning multiple sclerosis—its causative factors, its pathogenesis, its treatment—and yet to date we have been unable to determine definitely just what agent brings about this fairly common disease. That it is a chronic progressive condition of the central nervous system beginning in early adult life, with periods of temporary remissions, is an accepted fact. A number of theories dealing with the origin of multiple sclerosis have been advanced by different investigators, but despite this we are still in doubt as to the real cause of the disease. Among the possible etiologic agents submitted as causative factors are spirochetes, filtrable virus, myelolytic ferments, endotoxins and primary disease of the glia. According to Marie the condition is frequently observed as a sequel to some infectious disease such as typhoid, scarlet fever, etc., and he therefore assumes that the individual foci have an infectious inflammatory origin. This view has not been generally accepted. Oppenheim believes that multiple sclerosis is related to chronic intoxications and while his viewpoint has been endorsed by some, many other investigators have not ratified this theory.

Cases of familial multiple sclerosis are fairly uncommon, yet from time to time reports of such instances have appeared in the literature, and this leads one to believe that one theory at least may be tenable, viz., that it is of an endogenous nature, a primary multiple gliosis due to a congenital abnormal predisposition. Eichhorst¹ reported the case of a woman who contracted the disease prior to the birth of a son; the child later

developed multiple sclerosis and died at the age of nine. Two children, born before the mother displayed symptoms, did not suffer from the disease. Klausner² recorded a case in which a brother and sister suffered from this affection. Weisenberg³ reviewed 2 cases which occurred in a brother and sister who were born in England. Reynolds⁴ wrote about two families, in one of which an English sister and her two brothers were affected. Allen⁵ reported the disease in two sisters and a brother. Robinson and Robinson⁶ reviewed the history of a family in which 8 cases of multiple sclerosis occurred in three generations.

Of all the cases of multiple sclerosis that have come under our observation in the wards of the Jefferson Hospital during the past five years, we have never found the disease existing in more than one member of a family until the present instance. Cases of familial multiple sclerosis are rather unusual, and whether this condition should be grouped with familial diseases has not yet been definitely established.

The first case is that of J. M., a white male, aged thirty-seven, born in Ireland and a dyer by occupation. When the patient was nine years of age his mother had died in childbirth; his father, two brothers and five sisters were living and well. The family history was essentially negative for a similar condition. The patient was married; his wife was alive and well. There were three children, a girl of fourteen, a boy of thirteen, and a girl of ten. The eldest child later developed the disease; the other children have to date shown no symptoms of it. The patient's general health had always been good except for an attack of influenza in December, 1927. At the time of admission to the Jefferson Hospital in December, 1931, the man complained of difficulty in walking, pain and numbness in the right arm and leg, occasional attacks of frontal headache, constipation and sphincter disturbance. The condition was first noticed in 1928 because of soreness in the calves of both legs and a tight bandlike sensation around the waist. He had trouble in bending his legs, especially the right one; his lower extremities became more spastic and he dragged the right leg when walking. When examined in December, 1931, the station showed a marked Romberg and the gait was spastic. A bilateral horizontal nystagmus was present together with hyperopic astigmatism and some pallor of the temporal disks. The speech was of a peculiar slurring type. There was an intention tremor of the hands, and a slight decrease in the reflexes of the upper extremities. The grip on the right was weaker. Abdominal reflexes were lost, and there was sphincter disturbance. Both lower extremities were quite spastic. Patellar and Achilles reflexes were increased. Babinski sign was present on the right, very slightly so on the left. Oppenheim and Gordon signs were elicited on the right. Vibratory sense was

CLINIC OF DR. M. A. BURNS

FROM THE NEUROLOGICAL SERVICE OF THE
JEFFERSON HOSPITAL

MULTIPLE SCLEROSIS

IN recent years various authors have written more or less extensively concerning multiple sclerosis—its causative factors, its pathogenesis, its treatment—and yet to date we have been unable to determine definitely just what agent brings about this fairly common disease. That it is a chronic progressive condition of the central nervous system beginning in early adult life, with periods of temporary remissions, is an accepted fact. A number of theories dealing with the origin of multiple sclerosis have been advanced by different investigators, but despite this we are still in doubt as to the real cause of the disease. Among the possible etiologic agents submitted as causative factors are spirochetes, filtrable virus, myelolytic ferments, endotoxins and primary disease of the glia. According to Marie the condition is frequently observed as a sequel to some infectious disease such as typhoid, scarlet fever, etc., and he therefore assumes that the individual foci have an infectious inflammatory origin. This view has not been generally accepted. Oppenheim believes that multiple sclerosis is related to chronic intoxications and while his viewpoint has been endorsed by some, many other investigators have not ratified this theory.

Cases of familial multiple sclerosis are fairly uncommon, yet from time to time reports of such instances have appeared in the literature, and this leads one to believe that one theory at least may be tenable, viz., that it is of an endogenous nature, a primary multiple gliosis due to a congenital abnormal predisposition. Eichhorst¹ reported the case of a woman who contracted the disease prior to the birth of a son; the child later

Gordon signs, and right foot drop in addition to lost vibratory sense. Blood, spinal fluid, urine and roentgen-ray reports were negative.

In both the foregoing cases the condition advanced so rapidly that all attempts at further treatment were of little avail, and consequently it was finally necessary to transfer the father and daughter to the Philadelphia General Hospital for observation and custodial care.

The third case is that of a school teacher, A. P., white, female, aged thirty-one. She was admitted to the Jefferson Hospital on September 14, 1931, and discharged October 8, 1931. She complained of weakness in both legs and of a tight feeling in the soles of both feet, both symptoms being more pronounced on the right side. She was nervous, and it was impossible for her to walk without assistance. In addition there was a slight speech difficulty. The patient's father, aged sixty-nine, was living but suffered from heart trouble; the mother had died from pneumonia; three brothers and four sisters were living and well. The family history was negative for nervous or mental diseases, and there was no record of any cancer, typhoid or tuberculosis. During childhood the patient had measles, mumps, chickenpox and whooping cough. There was no history of pneumonia, typhoid fever, scarlet fever or rheumatic fever, but in March, 1931, she had an attack of influenza. During this illness she lost strength rapidly and was confined to bed for two weeks and could not return to work for a month. Her legs never seemed to regain their full strength and when the patient did return to school she found it necessary to grasp nearby objects for support when standing or walking. Her knees felt stiff and she walked with difficulty. She improved somewhat but in August, 1931, the weakness and stiffness in the legs began to grow progressively worse. Then a tight feeling in the soles of her feet was experienced, and the symptoms appeared to be more pronounced on the right side. On admission to the hospital in September, 1931, the patient could not walk alone; she had to be assisted by two persons. She had a markedly atactic, spastic gait, and because she was unable to stand without support the Romberg test could not be carried out. There was slight nystagmus, and the patient had some trouble in articulating. The upper extremities showed a slight intention tremor; the biceps and triceps reflexes were exaggerated bilaterally, but there was no evidence of Hoffman's sign. The abdominal reflexes were lost. In the lower extremities there was marked spasticity on both sides with bilateral increased patellar and Achilles reflexes, more accentuated on the right. There was bilateral Babinski and Chaddock signs, bilateral patellar and ankle clonus, and very pronounced incoordination in the heel-to-knee test on both sides. The vibratory sense in both lower extremities was lost. Blood and spinal fluid examinations proved negative. The eyeground report revealed a slight pallor of the temporal disks.

This patient received hyperpyrexia treatment by diathermy between September 14th and October 8th, and was discharged in a somewhat improved condition. She returned to her occupation of teaching on February 1, 1932, and has

decreased bilaterally. Blood Wassermann and Kahn were negative, as were the spinal fluid, urine and blood chemistry. The patient was given hyperpyrexia treatments by diathermy and left the hospital in an improved condition.

He was readmitted to the hospital on February 2, 1932, about one year later. No definite changes were noticed; he was not as spastic as formerly and walked more easily. The outstanding features were nystagmus, spasticity and increased reflexes of the lower extremities, together with a bilateral Babinski sign. Again laboratory reports proved negative, and the eye condition remained the same. Patient received a second course of ten diathermic treatments and was discharged in an improved condition. Since leaving the hospital he has remained at home, and his condition has become progressively worse.

The second case is that of E. M., elder daughter of the first patient, who developed the disease two years after her father had become ill, and whose condition progressed far more rapidly than did the parent's. The girl, a white female, aged fourteen, was born in Ireland. She was admitted to the Jefferson Hospital in January, 1932, because of inability to walk, speech difficulty, intention tremor of the hands, and inability to use them properly, diplopia and sphincter disturbance. Except for an attack of influenza in 1929 her general health had always been good. The onset occurred in January, 1930, when she came home from school one day feeling nauseated. After vomiting she remained at home several days and suddenly became cross-eyed. The condition was diagnosed as a paralytic internal squint of the right eye. In the summer of 1930 she had diplopia for two months. She returned to school and felt well until November, 1930, at which time her vision became dim and blurred to such a degree that she could not read. Refraction corrected this condition. In December, 1930, while at school she felt ill and dizzy and soon collapsed. For the next few weeks she was weak, nervous and tremulous. Following this she began to stagger when walking. In February, 1931, she began to have trouble in speaking; she hesitated and had great difficulty in pronouncing words. The gait gradually became more unsteady until by July, 1931, she could not walk without assistance. One of the first symptoms was weakness of the hands, especially in the right extremity. The hands were clumsy and erratic in movement. The speech grew more and more difficult to understand, and the tremor became progressively worse.

The important findings in this case were marked ataxia, coarse tremor of the head, nystagmus, difficulty in articulation, and in the upper extremities: marked weakness of the right arm and hand, bilateral decreased biceps reflexes, slightly decreased triceps reflexes and adiadokokinesis. The abdominal reflexes were lost. In the lower extremities both feet were deformed, there being high arch and instep with great toe extension. Weakness was present on both sides, but was more pronounced on the right. There were bilateral exaggerated patellar and Achilles reflexes, ankle clonus, Babinski sign, Oppenheim and

lost in both legs, and in these extremities there were involuntary spastic movements which the patient could not control. The eyegrounds showed a slight bitemporal pallor. The blood and spinal fluid Wassermanns were negative at both the Bryn Mawr and Jefferson hospitals. This patient also complained of some bladder disturbance which was, however, not a prominent symptom.

From May 7th to 16th she received her first course of artificial fever treatments, ten in number. During these she suffered a severe burn over the left breast which was very deep. No improvement in her condition was noticed. On June 26th a second series of fever treatments was instituted, and she received ten more treatments. After these her condition became somewhat improved although the lower extremities were still spastic and she still exhibited a positive Babinski and ankle clonus. It was impossible for the patient to walk without assistance, but she could manage to do so with the help of a nurse or by grasping the beds in the ward. On September 1st she was started on a third course of treatments, of which there were ten in number. The patient appeared very much improved after this, and by the middle of September she was able to walk with the assistance of a cane. She left the hospital on October 8th, still walking with a cane, but she was not quite so spastic.

At the present time this patient presents a very slight atactic, spastic gait, positive Chaddock sign, bilateral increased reflexes and bilateral ankle clonus. A slight nystagmoid movement is still present, and while her speech has improved very much, it is still somewhat slurring. Her improvement has been continuous since leaving the hospital, and for over a year she has been able to do her own housework. Although she still presents clinical signs she is able to come to the hospital alone, and I have shown her to various groups on different occasions.

The fifth case is that of F. A., white male, aged twenty-eight, a bookkeeper by occupation. In December, 1931, he complained of inability to walk, weakness of the hands, numbness around the pelvic area and occasional twitching of the feet. The father, mother and one sister were alive and well, and the family history was essentially negative except for the fact that both grandfathers had suffered from cancer. The patient had had measles, chickenpox, scarlet fever, mumps and diphtheria, and he had undergone a tonsillectomy. The general health had always been good, and there was no history of influenza or pneumonia. Eight years previously the patient had had an attack during which the symptoms were similar. It began with numbness in the right hand, and he was unable to hold a pencil in his fingers because of weakness. His legs felt weak and he staggered as though intoxicated. He also had a feeling of numbness in his left side. In about a month all the symptoms cleared up and he felt better. From then, 1923, until October, 1931, he remained well and had no return of symptoms except for occasional tingling and numbness in his hands. These were only present at periodic intervals. In October, 1931, he began to suffer weakness in the right leg; his left leg remaining normal. His right knee became so stiff he could not bend it. In a short time he was unable to walk. The left leg and knee, although not involved at first, soon became quite stiff and weak, and eventually were more affected than the right. Patient's hands felt very numb; motor power was deficient in both and more especially in the left hand. It was impossible for him to hold even a piece of bread. His right hand, while quite numb

taught continuously since that time. This young woman still presents a bilateral Babinski and ankle clonus in addition to nystagmus. The speech disturbance is not as marked as it was, and the vibratory sense has improved. The station and gait are very much better.

In these 3 cases one would be inclined to agree with Marie when he says that multiple sclerosis frequently follows acute infections such as typhoid, scarlet fever and others. In these cases it may have been that the influenza was the exciting cause in predisposed individuals. In the fourth case there is a history of pneumonia, but in the fifth case no record of any such infection could be obtained; therefore we should not want to maintain that the infection in the four other cases was of any fundamental value except as an exciting cause.

The fourth case is that of H. H., white, female, aged forty-two, married, who was admitted to the Jefferson Hospital on April 13, 1931, and discharged October 31, 1931. Her chief complaints were stiffness in the legs, difficulty in walking, numbness in the left hand and some difficulty in articulation. Her mother had died from diabetes; the father was living and well. Two sisters and two brothers were living and well; one brother had had a spastic condition of his side, but because it was impossible to examine this relative, it could not be determined whether or not he suffered from a hemiplegia. The patient had had five children and two miscarriages. Ten years before admission to the hospital she had influenza, and in March, 1930, she suffered an attack of pneumonia from which she made a good recovery. In June of 1930 she noticed difficulty in walking, and felt as if she had not sufficient strength. After a short time the condition cleared up, but in October of the same year she had a recurrence of weakness in the legs, a feeling of tightness in the hands and some difficulty in speaking. The trouble continued from October until January, 1931, when she again felt well. About March 1, 1931, she observed a sudden return of all symptoms; they were more severe at this time and she was unable to walk at all during the attack.

At the time of admission to the Jefferson Hospital, on April 13, 1931, the patient was unable to walk because of marked spasticity in both lower limbs; she had some trouble in articulating and there was weakness of the upper extremities. Station and gait could not be tested because of the patient's inability to stand or walk. The eyes revealed pupils which were equal and regular, but there was a slight nystagmoid movement when looking to the right or left. The speech was somewhat slurring in character. The upper extremities were slightly spastic, biceps and triceps reflexes were increased bilaterally, and there was a slight intention tremor. The abdominal reflexes could not be elicited because of a rather fat and flabby abdominal wall. The lower extremities were markedly spastic; the patellar and Achilles reflexes were greatly exaggerated, and there were bilateral ankle clonus, Babinski and Chaddock signs. Vibratory sense was

factor as regards institution of treatment by hyperpyrexia. If the case is one of a very advanced nature, we feel that resorting to hyperpyrexia would be more or less useless. Then, too, treatment of this kind is contraindicated in cases that have developed late in life. Patients in whom prolonged remissions are expected should be good physical risks and preferably under fifty years of age.

NOTE: Acknowledgment is gratefully made to my associate, Dr. B. P. Weiss of the Jefferson Hospital, for his views on the results of treatment of multiple sclerosis by hyperpyrexia.

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and tingling at times, was still stronger than the left and he was able to write with it.

Examination in January, 1932 showed a young adult male with definite difficulty in walking and with an ataxic, spastic gait. The Romberg sign was positive. He had bilateral lateral nystagmus, and there was some slight speech disturbance. In the upper extremities the grip was weak in both hands; the reflexes were somewhat decreased, and the finger-to-finger and finger-to-nose tests revealed some slight ataxia. The abdominal reflexes were lost. In the lower extremities both patellar and Achilles reflexes were exaggerated. He had bilateral Babinski, Chaddock, Oppenheim and Gordon signs. Motor power was markedly decreased. There was no loss of vibratory sense. The blood, spinal fluid and urine examinations all were negative. The eyeground report showed a slight bitemporal pallor.

This patient was admitted to the Jefferson Hospital on January 6, 1932, and was discharged January 25, 1932. Hyperpyrexia was administered in ten daily treatments, and the patient left the hospital in a markedly improved condition. He is still under observation and since January, 1932, he has not had a recurrence of any symptom whatever except for a slight ataxia. He is active, able to work, does not complain of any of his former symptoms except a slight awkwardness in gait which is barely perceptible to an impartial observer.

Our interest in multiple sclerosis is twofold; we are concerned first with the possibility of an infection, not yet definitely isolated, having an etiologic influence on the pathologic process, inasmuch as four of the cases reported gave a history of infection just preceding the initial symptoms of the disease. Secondly, we are interested from the standpoint of treatment by hyperpyrexia. We are probably dealing with a chronic infectious process induced by metabolic or toxic change. It occurred to us that if we could create a febrile state in patients of this sort we might increase the ferment and antibody reactions so as to neutralize the toxic influence of the condition and prevent further degeneration of the affected neurons. Such a measure would alleviate symptoms and bring about a remission. The remissions obtained thus far by hyperpyrexia have generally been so marked and of such prolonged duration that we feel much has been accomplished in the forward treatment of multiple sclerosis. We have in use now a new apparatus for the production of fever, the hyperpyrexator, in which there is no risk of burns or any other contraindication, and in which the patient is quite comfortable except for the usual febrile state. Rapidity of onset in multiple sclerosis is a favorable

QUESTION.—Is there any other reason why the breath sounds should have been absent?

STUDENT.—Yes, the lung has been compressed by the air in the pleural sac.

Anteriorly over the precordium "sticky" râles were present and a peculiar crackling sound was heard which seemed to be exaggerated by breathing although also present when respirations were momentarily halted.

The tinkling metallic character of the heart sounds persisted.

At 6 P. M. on February 10, 1932, after having spent the most comfortable day since admission, the patient suddenly began to moan and grow restless. She became pale and cyanotic, her pulse rate rose, air hunger developed and she suddenly expired at 6.30 P. M.

The cause of this sudden change was somewhat of a mystery until we viewed the autopsy performed by Dr. Benjamin A. Gouley, from whose report we summarize the following:

"The body is that of a young woman, showing contusions over various portions of the body and especially over the left lateral aspect of the chest.

"On removing the breast plate and incising the exopericardium and adjacent mediastinal tissue, a gush of air escaped. The mediastinal tissues contained numerous air bubbles. On the left aspect of the exopericardium, near the apex, there was a tear in the tissue. This communicated with the pleural cavity but did not seem to extend into the pericardial sac.

"The left pleural cavity was entirely filled by a massive hemorrhage. The lung was entirely collapsed within this hemorrhage. On removing this blood, the fourth, fifth, sixth and seventh ribs were found fractured, each in three places. The fractures were jagged and diagonal, so that sharp, elongated fragments protruded inwardly, pointing to the anterior aspect of the lung. The collapsed lung presented numerous tears in the pleural surface.

"The heart was pushed over toward the midline. There were signs of an acute low-grade interstitial myocarditis."

From these findings it was apparent that the pathologic signs in the lungs were due to a hemopneumothorax as was suspected. The heart damage, though not as definite, indicated that air had entered the exopericardium. In addition, it was evident that we were dealing with an acute interstitial emphysema of the mediastinum and it seemed most likely that thus air had entered the pericardial sac itself.

As to the sudden demise of the patient, it would seem that the jagged broken ribs were repeatedly tearing into the lung on any slight motion produced by deep respiration or cough. The final exitus was due, in the opinion of the pathologist, to massive intrathoracic hemorrhage which compressed the lung, and by displacing the heart, seriously impaired its function.

CLINIC OF DRS. JOSEPH C. DOANE AND MAURICE S. JACOBS

FROM THE MEDICAL SERVICE OF THE JEWISH HOSPITAL

PNEUMOHEMOPERICARDIUM; RHEUMATIC AND LUETIC HEART DISEASE

We desire today to present 2 unusual cases.

PNEUMOHEMOPERICARDIUM

The first patient, Mrs. L. H.,* aged twenty-three, was admitted to the Jewish Hospital at 3 A. M. on February 6, 1932, with a provisional diagnosis of fractured ribs, pleural hemorrhage and shock. These injuries were sustained a short time before as a result of a vehicular collision.

Upon the initial examination the patient was found to be unconscious and presented many contusions of the body generally and especially over the left chest. The respirations were hurried and difficult, the pulse rapid and thready, and the pallid skin and mucous surfaces were bathed in perspiration. The percussion note was hyperresonant over the entire left hemithorax. The heart rate was 140 and a curious tinkling sound was heard with each beat.

At 10 A. M. she was seen by us for the first time. The patient was still unconscious, cyanotic and very dyspneic. The blood pressure was 80 over 40 mm. Hg. The temperature was 102 F., the pulse 150. There were definite signs of air and fluid in the left pleural cavity and from the nature of the accident a provisional diagnosis of left hemopneumothorax was made.

QUESTION.—What may produce this condition?

STUDENT.—Puncture of the lung by the sharp edges of a broken rib.

QUESTION.—What are the classical signs of air and fluid in the thoracic cavity?

STUDENT.—Hyperresonance above, changing to dulness below. A positive coin test, metallic tinkle and a succussion splash upon the quick alteration of the patient's position.

In addition to these pulmonary signs another bizarre sound was heard. Over the precordium, a peculiar beating was heard not unlike the slapping sound of fluid in a bottle when the contents are agitated. This was synchronous in time with the tinkling sound just mentioned. This sign we believed pointed to the existence of a hemopneumopericardium.

During the next three days the patient slowly began to recover.

On February 9th examination revealed a tympanitic note anteriorly over the entire left chest, but dulness existed at the base. The breath sounds as well as the vocal fremitus were much diminished over this area.

* Reported through the courtesy of Dr. Moses Behrend.

(a) Those in which the pericardium has been punctured as a result of trauma to the chest wall or to the esophagus with the resulting ingress of air.

(b) The infection of a pericardial fluid and the production of a gas as a result.

(c) Those resulting from the perforation into the pericardial sac of an ulcer or abscess in the esophagus, lung, pleura, stomach, liver or the rupture of an infected pericardium into any of these structures.

(d) The deliberate introduction of air for therapeutic purposes or the accidental creation of a temporary fistulous connection between the lung and the pericardial sac during a thoracentesis.

In 5 out of 7 cases collected by Gottesman and Benedick,³ air in the pericardial sac resulted from the development of ulcerative fistulous tracts leading from surrounding organs. Foreign bodies in the esophagus, pleura, lung, a liver abscess or a gastric carcinoma furnish excellent examples of this type of original causative pathology. It is interesting to note in passing that in animals, puncture of the pericardium by foreign bodies in the stomach and esophagus is rather common. This is particularly true in cattle and in the ruminant inhabitants of zoological gardens.

The symptoms of this condition are not characteristic but the physical signs are almost pathognomonic. Dulness over the precordium giving way to tympany on change of position or the existence of a tympanitic note above with lower dulness over the left anterior chest should arouse the examiner's suspicion of the existence of air and fluid in the pericardium. If on auscultation a metallic, splashing, gurgling or churning sound is heard synchronous with the contraction of the heart, a diagnosis may almost certainly be made. This is the "bruit de moulin" of Brichetau or the "bruit de la roue hydraulique" of other writers. The succussion splash is often so loud that the patient complains of its presence and the physician may hear it without applying the ear or the stethoscope to the chest. To be sure, there are other conditions which may produce a

Comment.—The term “pneumopericardium” formerly was loosely employed to indicate that not only air but also a serous or purulent fluid was to be found in the pericardial sac. This usage is hardly to be recommended since the terms “hydro-pneumopericardium” and “pyopneumocardium” are at once more descriptive of the actual condition. Moreover, the presence of a serous or purulent fluid in this cavity is a somewhat more common occurrence than is the presence of a gas alone. Brichetau reported the first case of pneumopericardium in 1844 and it was this observer who coined the term “bruit de moulin” or water-wheel bruit as descriptive of a most interesting auscultatory physical sign usually found in this condition. But in the next eight decades relatively few cases found their way into medical reports. Indeed, Heise and Lawrason Brown¹ in 1924 stated that pneumocardium is of such rarity that it amounts in reality to a curiosity when discovered. A search of the literature today, however, hardly justifies this statement, although the condition is far from common. These writers were able to discover but 45 cases of pneumopericardium in the literature up to a decade ago. Wounds of the cardia and its coverings are more common. I. A. Bigger² in 1932 stated that in seventy instances wounds of the pericardium and heart muscle had been treated surgically. In this series the presence of a pneumopericardium was mentioned but twice, both of these cases being reported by Bigger himself. Curiously enough prior to 1903 but thirty-seven instances of this condition had found their way into the literature of medicine, a number of which had been discovered at the postmortem table.

The etiology of pneumohydropericardium is of much interest. Rarely is air found in the pericardial sac without the added presence of fluid. A notable exception to this statement is found in those instances when a gas is introduced into this sac for therapeutic purposes in the treatment of an inflammation of the pericardium. Air is sometimes employed to replace fluid which has been withdrawn. But trauma from without is not always causative. Generally speaking patients suffering from a pneumopericardium fall into four etiologic classes.

and able to lie in the dorsal decubitus without embarrassment. There was marked pulsation of the carotid vessels, a systolic bruit was heard over both vessels and a thrill was definitely felt in the supraclavicular fossa. The superficial veins of the neck and thorax were engorged.

The area of cardiac dullness extended almost to the anterior axillary line. The right border of the heart was percussed 5 cm. to the right of midsternal line and the base was widened to 5.5 cm.

A blowing systolic and diastolic murmur was heard over the mitral valve area. A double murmur was also present over the base, the systolic element of which was transmitted to the vessels of the neck. There were visible epigastric pulsations and the liver was enlarged to three fingerbreadths below the costal cage. All the peripheral vessels pulsated strongly.

QUESTION.—What is the usual anatomical heart lesion which produces such marked pulsations?

STUDENT.—Aortic insufficiency and arteriosclerosis.

QUESTION.—What other evidence of this lesion do we have in the peripheral vascular system?

STUDENT.—The collapsing pulse, the pistol-shot sound over the femorals and Duroziez's murmur.

All these were present. The blood pressure readings were instructive. In the right arm, the blood pressure was 140 over 40 mm. Hg. Over the right femoral artery, the readings were: 230 over 50. Such readings are quite characteristic of the loss of the vis-a-tergo associated with insufficiency of the aortic valve.

It was obvious then, that we were dealing with a condition characterized by a slowly failing myocardium, yet certain of the common signs of cardiac decompensation were absent.

QUESTION.—What are some of these signs?

STUDENT.—Swelling of the legs, congestion of the lungs with dyspnea and cyanosis.

Yes, and these are just the signs he did not show. Why?

STUDENT.—The signs of decompensation depend upon which side of the heart is chiefly damaged.

That is correct. If the right side fails, the signs evidenced are pulmonary congestion or even hemoptysis. The liver may be swollen and tender, ascites occasionally occurs and ankle edema is present.

If the left side fails these symptoms may be absent. The patient may only exhibit progressive weakness and inability to perform accustomed work. Nocturnal attacks of cough or suffocation are quite common and anginoid types of pain are present.

QUESTION.—What else should we know to determine the type of heart disease present?

STUDENT.—The etiology, especially as to the previous occurrence of rheumatic or venereal infection.

We turn to his past medical history to see if any light can be shed upon this point. The only record of any of the rheumatic-streptococcus group of diseases was the incidence of frequent attacks of tonsillitis. The patient denies having had lues nor is there evidence of a penile scar. This, however, does not exclude

simulation of these signs. The most noteworthy are hydro-pneumothorax and mediastinal emphysema. In this patient the characteristic tinkling, and the metallic quality of the heart sounds were at once indicative of the diagnosis.

When considerable blood collects in the pericardial sac, the heart sounds are of course muffled, the dimensions of the heart widened and the cardiohepatic angle becomes obtuse. If the hemorrhage is profuse, tamponade of the auricles with distention of the cervical veins occurs and death ensues. Hydro-pneumothorax may exist in both traumatic and ulcerative cases as an accompanying condition. When air and fluid exist in the pericardial sac, however, the succussion and other adventitious sounds are louder, are heard best over the heart area and there is shifting dulness on alteration of the patient's position.

The presence of an excessive amount of air and fluid in the pericardial sac may rapidly cause death. An immediate tapping or a rapid opening of the costal cage with relief of the pressure is often life saving. In the patient under consideration, a massive hemorrhage into the pleural sac brought about dissolution. Finally, to remember to search for the presence of a hemopneumopericardium is often to arrive at a fairly obvious diagnosis. The urgency of symptoms arising from the obstruction of the vessels entering or leaving the heart or a resultant interference with the functioning of its chambers will determine the necessity for the surgical relief of intrapericardial tension.

RHEUMATIC AND LUETIC HEART DISEASE

The second patient we wish to discuss with you today is one whom you studied several weeks ago. You will recall the case of Mr. H. S., who was first admitted to this hospital on February 16, 1932. At that time he complained of weakness, cough, loss of weight and breathlessness on exertion.

These complaints had been developing gradually over a period of several years. He also found it increasingly difficult to climb stairs or walk a half dozen blocks. When he persisted, he developed a pain in the left shoulder which was relieved by rest.

QUESTION.—What is your impression of the history thus far?

STUDENT.—It seems to point to a slowly developing failure of the heart.

That is correct. Now let us recall the salient facts revealed by our examination of the patient at that time. He was middle-aged, without cyanosis or dyspnea

After two weeks' stay in the hospital the patient's symptoms had largely abated and he was referred to the care of his family physician. For one week he remained in good condition but then distressing congestive symptoms began to appear.

On April 7, 1932, he was readmitted to the hospital. Today you observe that the patient is moderately cyanotic and orthopneic. All peripheral vessels are tortuous and pulsating. There is dullness over the left lung posteriorly, extending from the base to the seventh dorsal vertebra. Vocal fremitus is absent here. The breath sounds are diminished over this area and a few crackling râles are heard over both bases.

The heart is somewhat widened at the base. The left border is obliterated by the presence of fluid in the left chest. The right border extends 5 cm. to the

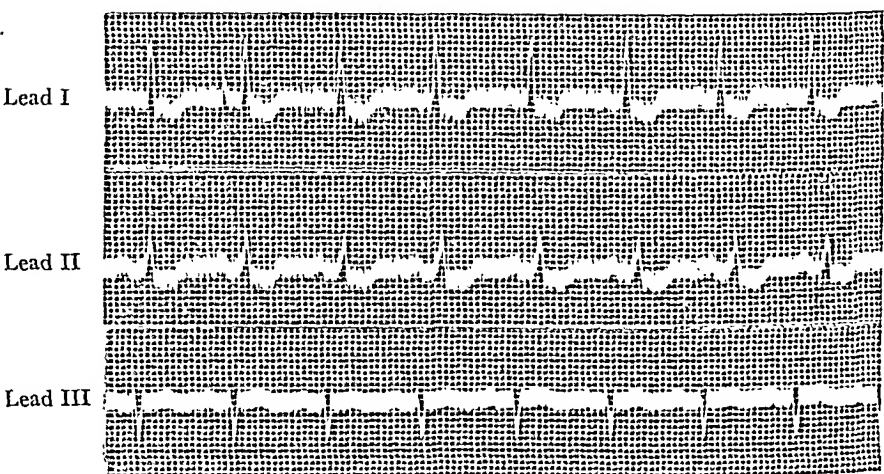


Fig. 115.—Electrocardiogram taken 4/12/32. Rate 98, regular. Slurring of QRS all leads; inversion of T waves in leads I and II. Deviation of RS-T interval leads I and II, suggesting coronary occlusion.

right of the midsternal line. A double murmur is heard over the aortic area transmitted to the vessels of the neck and down the left border of the sternum. At the third left interspace a short murmur late in diastole is heard while at the apex, a blowing systolic murmur is present.

The liver is three fingerbreadths below the costal border. A small amount of fluid is present in the flanks. Edema of the lower extremities is present. As you observe, it extends above the ankles.

Two days after admission, after spending a fairly good night, he had an attack of dyspnea and sharply localized precordial pain. Within a few hours, a loud to-and-fro friction rub was discovered in the fifth interspace at the sternum which later extended out into the axilla.

QUESTION.—What, in your opinion, was the nature of this new development?

STUDENT.—It would seem that pericarditis had set in.

the presence of lues inasmuch as our physical signs point to the presence of aortitis and aortic insufficiency which are predominantly luetic in origin. When the laboratory reported a plus 4 Wassermann reaction we were not surprised.

The patient was in the ward for two weeks, under absolute bed rest, iodides, sedatives, and an aqueous bismuth solution, given intramuscularly.

STUDENT.—May I ask why, if the patient had an aortic regurgitation of such a marked degree, there was not a greater hypertrophy of the heart, especially of the left ventricle?



Fig. 114.—x-Ray of chest, 2/17/32, showing slight cardiac enlargement. There is mitralization of the left border, and enlargement of the right heart. G. V., 5.2 cm.; M. R., 5.6 cm.; M. L., 7.5 cm.; thorax, 27 cm.

That is a good question and one that we will take up in a moment. You will recall that a mitral systolic and diastolic murmur were present. Although the typical crescendo presystolic murmur was absent the definite double murmur at the mitral valve led us to diagnose mitral endocarditis of rheumatic origin. When aortic insufficiency is present alone, it produces a marked enlargement of the heart to the left; when combined mitral disease is present by itself, enlargement of the right heart follows: when the two are both present, they compensate each other and do not lead to such marked hypertrophy (Fig. 114).

were performed, thirteen times on the left side and five times on the right side, yielding 8000 and 2700 cc. respectively, making the staggering total of 10,700 cc. of exudate removed (Fig. 116).

The patient grew progressively weaker and on April 27th, he died. The autopsy was performed by Dr. Benjamin A. Gouley, from whose report we summarize the following:

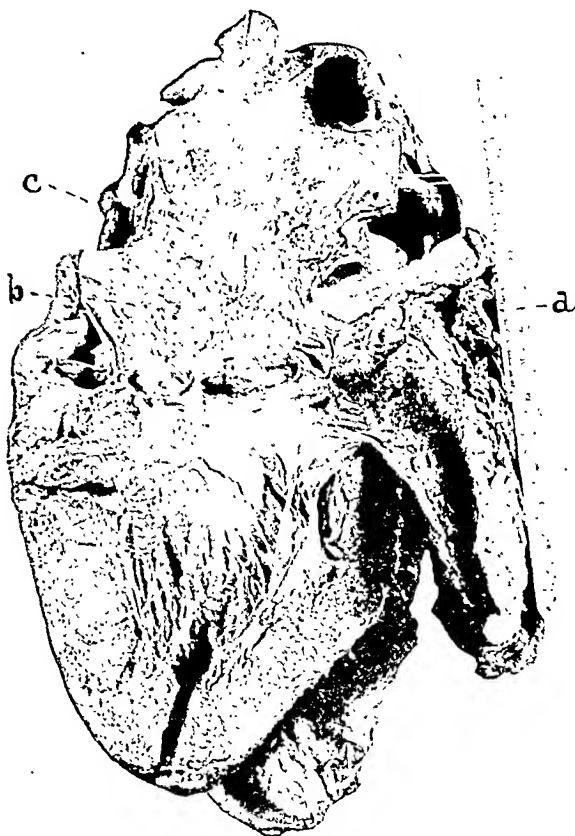


Fig. 117.—Photograph of heart showing acute, fibrinous (bread and butter) pericarditis (a) ; luecic aortitis (b) ; slightly dilated aorta (c).

Considerable adhesions were present anteriorly in both pleural sacs. A small amount of fluid was present in the left pleural sac.

Heart: The exopericardium was red, thickened and adherent to the mediastinal pleura, the sac extending almost to the anterior axillary line. Incision revealed a heavy, "bread and butter" pericarditis covering the entire pericardial surface. The surfaces were glued together, thick, shaggy and dark grayish-red.

QUESTION.—Do we have an etiologic background for this?

STUDENT.—The acute pain and dyspnea, and the subsequent finding of a to-and-fro friction rub might point to acute coronary occlusion. The pericarditis might be easily explained on that basis.

Some of the other signs of this accident, however, were absent. On the other hand, the rheumatic nature of the mitral lesion must be considered, since we know that pericarditis occurs frequently in the terminal stages of rheumatic endocarditis.

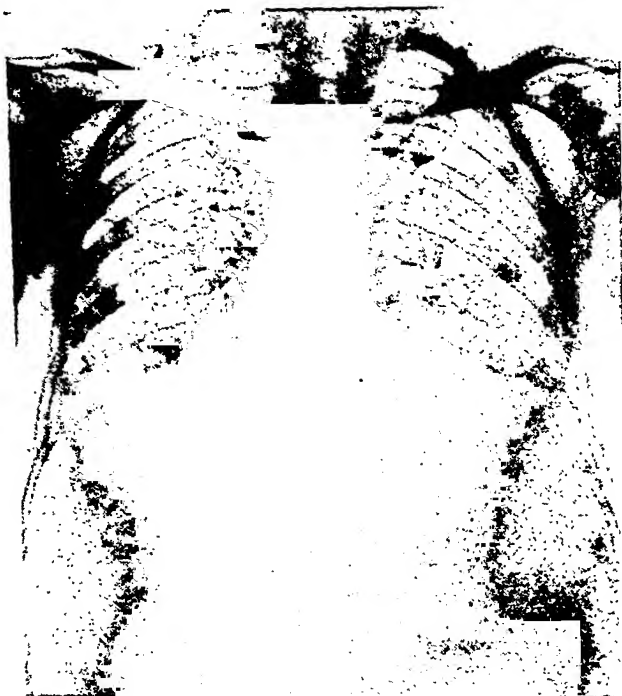


Fig. 116.—x-Ray of chest, 4/16/32, showing bilateral effusion, obliterating the cardiac silhouette. The base of the heart is slightly wider than in Fig. 114.

Let us examine the electrocardiogram (Fig. 115) to see if any additional light can be shed on this. As you see it does show some evidence of coronary artery disease.

In addition, a curious grating sound was heard in the right upper quadrant immediately below the costal margin. These interesting signs we can demonstrate to you today. We will render a further report on this case at our next meeting.

Concluding Report.—An increase in the amount of the fluid in the left pleural sac was noted on April 10, 1932, and 500 cc. of serous fluid were removed. This reaccumulated so rapidly that thoracentesis had to be performed almost daily on alternate sides. Between April 10th and April 27th, eighteen chest punctures

a very rare occurrence. It may be remarked in passing that while the pathologist who performed the autopsy and for whose opinion we have the greatest regard is firmly of the belief that such was the case, certain of his colleagues were inclined to doubt this finding. Nevertheless, all agreed that the aortic and myocardial pathology were typical of a luetic process and that the mitral lesion was undoubtedly of rheumatic origin. The etiologic factors concerned in producing aortic and mitral disease are well illustrated by this patient. The rarity of rheumatic involvement of the aortic valve alone is a well-recognized fact—only 5 per cent of all cases are of this etiologic type. In about one third of all cases of rheumatic endocarditis does one find both these valves the site of disease. In the opinion of some, rheumatic disease of both aortic and mitral valves signifies that the patient has suffered two separate and distinct attacks of rheumatism and that disease of the semilunar valvular elements has followed that of the mitral valve as a secondary process.

It is interesting to note that the signs of pericarditis developed but a short time before death. Nevertheless, this condition, as has been suggested elsewhere, no doubt played some part in determining the outcome of this case.

Progressive left heart failure was the cause of many of this patient's symptoms as his disability increased. Ample reason for the exhaustion and ensuing degeneration of the muscle of the left ventricle had existed for years in the presence of aortic and mitral disease. Weakness, dyspnea, particularly and increasingly nocturnal in type, duskiness of the cutaneous and mucous surfaces and a general failing of physical and mental powers are symptoms which point to the left-sided heart failure. Perhaps the first warning of cardiac distress is manifested by the presence of dyspnea. In this patient, because for many months the lesser circulation was more or less efficiently maintained, dyspnea was not distressing. Before death, however, when pulmonary congestion and hydrothorax developed the most distressing and obstinate symptom was dyspnea. The discovery of a fairly marked sclerosis of the pulmonary artery

The plasticity was most pronounced around the root of the aorta where the opposing surfaces were separated with some resistance, an almost complete blocking of the orifice of the right coronary artery having resulted from the luetic process. Without going into further detail, be it said, that there was found a definite luetic myocarditis and aortitis, aortic regurgitation and an old post-rheumatic mitral endocarditis (Fig. 117). The liver was enlarged and congested, the capsule was thickened and opaque.

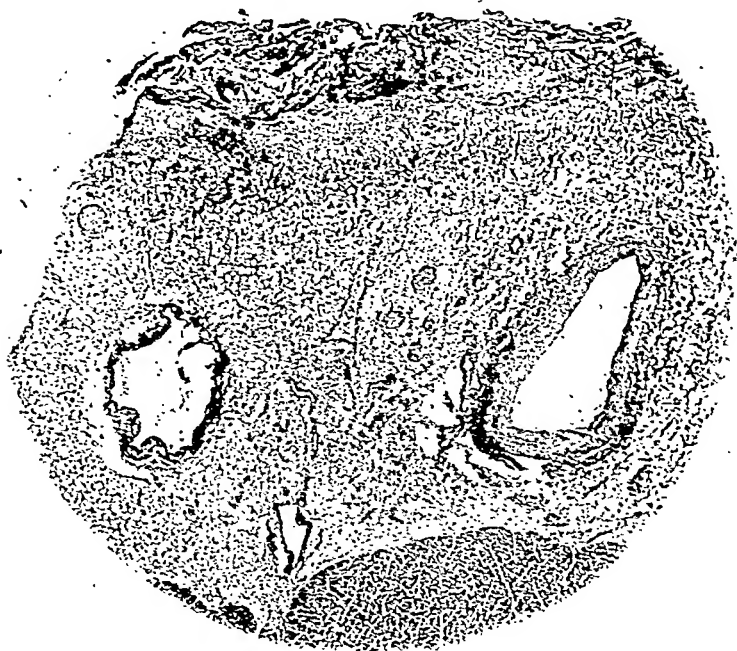


Fig. 118.—Microphotograph of section of heart muscle showing acute pericardial exudate.

It was the opinion of the pathologist that the acute, plastic pericarditis was syphilitic in origin despite the fact that this is regarded as a very rare condition (Fig. 118).

Comment.—This case presents several very interesting angles. In the first place the combination of rheumatic and syphilitic heart disease is rather unusual. Particularly is the finding of what appeared to be spirochetes in the pericardium

a very rare occurrence. It may be remarked in passing that while the pathologist who performed the autopsy and for whose opinion we have the greatest regard is firmly of the belief that such was the case, certain of his colleagues were inclined to doubt this finding. Nevertheless, all agreed that the aortic and myocardial pathology were typical of a luetic process and that the mitral lesion was undoubtedly of rheumatic origin. The etiologic factors concerned in producing aortic and mitral disease are well illustrated by this patient. The rarity of rheumatic involvement of the aortic valve alone is a well-recognized fact—only 5 per cent of all cases are of this etiologic type. In about one third of all cases of rheumatic endocarditis does one find both these valves the site of disease. In the opinion of some, rheumatic disease of both aortic and mitral valves signifies that the patient has suffered two separate and distinct attacks of rheumatism and that disease of the semilunar valvular elements has followed that of the mitral valve as a secondary process.

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may point to another factor which produced some of his congestive symptoms. It will be recalled that Ayerza and Warthin have described a condition in which luetic sclerosis of the pulmonary artery associated with polycythemia produces a very marked cyanosis as suggested by the term "cardiacos negros." There was no unusual increase, however, in the red cell count in this patient.

Of the greatest interest from the standpoint of pathologic physiology is the fact that an immense amount of fluid was removed from the pleural sacs and particularly, that of a total of almost 11 liters, 8000 cc. came from the left side. In cardiac disease when fluid collects in the pleural sac, the right side is most often the site of the hydrothorax, or if the condition is bilateral, the fluid level on the right side exceeds that on the left. Many explanations for this fact have been offered. Compression of the azygos vein by a dragging downward of the vena cava is a popular theory which to many, however, does not appear convincing. It is probable that in this case, pressure on the pulmonary veins by the dilated right auricle accounted for the fluid in the right chest. But the massive left-sided effusion demands explanation. We believe that the mechanism here is very similar to that to which reference has just been made, *i. e.*, a markedly dilated left auricle and ventricle sufficiently compressed the left pulmonary veins to cause a rapid collection of fluid in the left chest. It is within the range of possibility, moreover, that the developing pericarditis and the mediastinal adenopathy may have assisted in compressing these venous radicles at the root of the lung and thus aided in producing this unusually massive effusion.

The occurrence or the friction rub shortly before death was somewhat surprising, although pericarditis is one of the conditions most frequently overlooked by the clinician. In a recent comparison by one of us⁴ of the clinical and autopsy findings of 354 patients who died in this hospital, in 8 instances the presence of a pericarditis was unsuspected before death. You will remember that about a fortnight before death this patient complained of a sudden, acute, lancinating pain over the

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precordium. The electrocardiograph suggested the presence of acute coronary occlusion. The report of the pathologist, however, indicates that the obstruction of the coronary vessels was of long duration and consisted of a gradual encroachment upon their orifices by the luetic process.

Of usual interest and rarity was the discovery of a friction rub heard over the surface of the right lobe of the liver. You will remember that the pathologist pointed out the fact that the capsule of the liver was thickened and opaque. No doubt the grating sound above described was due to contact between the roughened capsule covering the anterior hepatic surface and the parietal peritoneum as the liver moved during respiration.

SUMMARY

We have presented today 2 rather unusual cases. In the first, the presence of air and fluid in the pleural and pericardial sacs and the tissues of the mediastinum gave rise to some interesting and at the same time very distinctive physical signs.

The second patient illustrates the following facts:

1. Left-sided heart failure may exist in some degree without displaying strikingly those signs and symptoms ordinarily thought to be diagnostic of decompensation.

2. Rheumatic and luetic heart disease may exist in the same patient. The finding of the spirochete in the pericardium, though very rare indeed, was reported by the pathologist.

3. The mechanism of the production of hydrothorax was discussed and the explanation of the occurrence of a massive left-sided collection of fluid was attempted.

4. An interesting friction rub heard over the anterior surface of the liver prior to death was explained by the pathologist.

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pregnancy we find individuals with reduced acid, some with very low acid, and some in which the free hydrochloric acid is totally absent. Certain patients have a total absence of the so-called "intrinsic factor" of Castle so important in the cases of Addisonian anemia.

Active and chronic active infection, and essential bone marrow deficiency are factors that cannot be excluded from an etiologic consideration. One must keep in mind, also, that as far as blood formation is concerned two are to be provided for

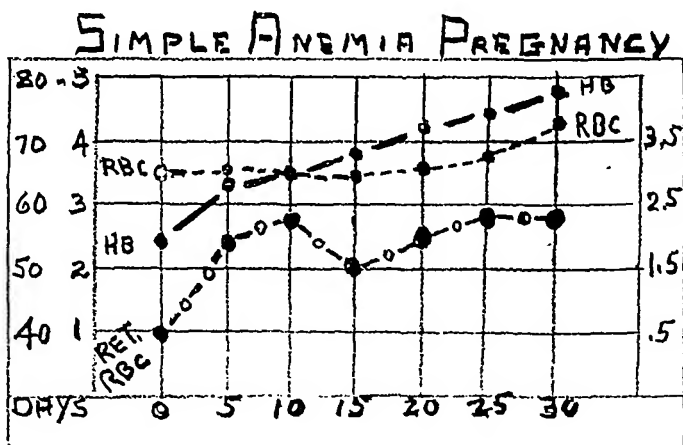


Fig. 119.—Simple anemia of pregnancy. Treatment started at the beginning of the eighth month. Reduced iron—30 to 60 grains daily—resulted in a reticulocyte response and an increase in hemoglobin and red blood cells which persisted throughout the remainder of the pregnancy. The appetite and general well-being of the patient were favorably affected.

instead of one. This fact alone is often sufficient for the development of the so-called "simple anemia." One of our patients in the fifth month of pregnancy had a hemoglobin of 70 per cent, red blood cells 3,500,000. There was little change until the eighth month, when the hemoglobin was found to be 58 per cent and the red blood cells 3,200,000. A good result followed the administration of iron.

The great majority of individuals, both male and female, have not as yet advanced to a point at which they seek a physical check-up twice a year. Any patient may develop an anemia

CLINIC OF DRS. HAROLD W. JONES AND LEANDRO M. TOCANTINS

FROM THE DEPARTMENT OF MEDICINE, JEFFERSON MEDICAL
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FUND

THE ANEMIA OF PREGNANCY AND ITS TREATMENT

THE recent years have brought revolutionary changes in our conception of the anemias from the standpoint of etiology, classification and treatment. In the past thought was directed toward some hemolytic agent as an etiologic factor. Now we discuss etiology in terms of vitamins, mineral deficiencies, and gastro-intestinal function.

The classification of the anemias of pregnancy is as follows:

1. Simple.
2. Severe.
3. Severe which is "pernicious" in type.

1. SIMPLE ANEMIA OF PREGNANCY

It has long been said that the anemia of pregnancy is physiologic. Such a statement, in view of our knowledge of the causes of anemia, is open to question. Keeping in mind the fact that it is possible for normal individuals to develop an anemia during the course of the year, which might erroneously be called physiologic, it is not difficult to understand the ease with which a pregnant patient becomes anemic.

It may be true that the simple anemia of pregnancy occurs as a result of increased blood volume, but this may be a minor cause. Probably the most important single cause for the anemia of pregnancy is insufficient diet. Second to this is gastro-intestinal disturbance. The amount of free hydrochloric acid and total acid in the gastric secretion bears some relation to the utilization of foods necessary for hematopoietic stimulus. In

blood count gradually reduced until it was found to be hemoglobin 55 per cent, red blood cells 2,800,000, and white blood cells 5400.

Diet.—Certain obstetricians have pointed out that a low protein or protein-free diet is important in the prevention of the toxemia of pregnancy. The low protein or protein-free diet, or the red-meat-free diet of the clinician is partly responsible for such a belief. The red-meat-free diet or low protein diet has been utilized by clinicians in the treatment of nephritis in the past and still is in some instances.

Today there is seldom a place for the protein-free diet in the treatment of nephritis. Almost without exception nephritics should have $\frac{3}{4}$ to 1 Gm. of protein per kilogram in their diet. Then, too, there is no reason why red meat should be excluded. Furthermore, we know that if the total protein is less than 4 per cent, edema develops in most cases. Frequently, if the total protein is low, and especially if there is a reversal in the albumin-globulin ratio, a high protein diet, $1\frac{1}{2}$ to $2\frac{1}{2}$ Gm. per kilogram is indicated.

The pregnant woman has been instructed by many physicians, and still is, to partake of a diet low in protein and particularly low in red meats. Such a régime is supposed to lessen the renal load and help prevent the occurrence of toxemia. No scientific reason has been set forth to support such a conclusion. The pregnant woman, even more than the normal woman, demands a reasonable amount of protein per kilogram ($1\frac{1}{2}$ to 1 Gm.) for the development of energy and the stimulation of cellular activity and metabolism.

The part that vitamins play in anemia has been well established. As has been pointed out by Castle and others, a high vitamin diet is of great importance in the treatment of cases of sprue. From our studies it would seem that a high vitamin diet is of value in the prevention and treatment of purpura. Many have stated that those who continue to live on a diet low in vitamin develop an anemia. Therefore, it would seem that a suitable diet for the average pregnant woman is one that contains moderate protein, is high in vitamin and low in fat. A diet which meets these requirements is set forth in this chart.

without symptoms. If such an individual becomes pregnant, this anemia continues or may be exaggerated. In most instances pregnancy is set forth as the cause of the entire anemia. One of my patients whom I saw for gastric distress had a blood count as follows: Hemoglobin 72 per cent, red blood cells 3,720,000, white blood cells 6800, and differential normal. A short time later she became pregnant, and was returned to me in her seventh month of pregnancy because of shortness of breath. At this time I found her blood count to be 60 per cent hemoglobin 3,400,000 red blood cells and 7200 white blood cells. The obstetrician felt that this was a rather marked reduction in hemoglobin, and it would have been considering 90 per cent is normal, but as she had been ambulatory with her hemoglobin approximately 72 per cent before pregnancy, the reduction was not marked.

There is another group whose anemia is more marked—60 per cent or less—that frequently withstand pregnancy badly. A patient with mitral insufficiency and hemoglobin of 60 per cent, red blood cells 3,660,000, became pregnant against our advice, and at the fourth month, in spite of dietary régime and hygiene, her hemoglobin had dropped to 46 per cent, red blood cells 2,500,000, and white blood cells 3200. The prominent symptoms in this case were dyspnea, marked edema of the extremities and the sensation of exhaustion, particularly in the afternoon. Under active treatment, which will be described later, she was improved.

Some pregnant women who already have an anemia may develop an infection, such as tonsillitis, la grippe, influenza, sinus disease, pyelitis, cholecystitis, gastro-enteritis, etc. To the patient already anemic, add pregnancy and infection and a more marked anemia may result. A woman, twenty-eight years of age, multiparous, presented herself in her second month of pregnancy, with a hemoglobin of 74 per cent, red blood cells 3,600,000, and white blood cells 7800. The third month the hemoglobin was 74 per cent, red blood cells 3,380,000 and white blood cells 6800. At this time an acute attack of la grippe developed. She was in bed for a week, and following this the

Sunlight.—If possible, the patient with simple anemia should be able to enjoy a reasonable amount of moderate exercise in the sunlight. If this is not feasible, the ultraviolet ray should be used for one to five minutes, general body exposure, at 30 inches, two or three times a week or daily in some cases. This treatment, in addition to dietary measures, aids in increasing the hemoglobin and red cell content. There is a question whether this is brought about by direct cell stimulation or indirectly by action upon the bone marrow and calcium metabolism. At any rate, some of the patients with moderate simple anemia are benefited by the use of these two measures.

2. SEVERE ANEMIA OF PREGNANCY

Possibly the differentiation between simple anemia of pregnancy and the severe anemia is somewhat academic, because so often the simple anemia becomes the severe anemia. The term is used to point out the difference between the anemia of pregnancy that is hypochromic microcytic in type and the severe anemia of pregnancy which is hyperchromic macrocytic or pernicious in type. In an arbitrary manner one may state that we are dealing with the so-called "severe anemia" of pregnancy when the hemoglobin is 45 per cent or less, and the red cells below 3,500,000. The important point, however, is not so much to differentiate between the simple and severe types of anemia as to differentiate these types from the pernicious anemia of pregnancy, because the treatment is dissimilar.

Etiology.—The causes of the severe anemia of pregnancy are similar to those discussed under the head "Simple Anemia," but special emphasis must be placed upon gastric secretion. As we have already stated, 50 per cent of the women with anemia of pregnancy have a low or absent free hydrochloric acid, even after histamine stimulation. Individuals with an anemia of pregnancy and an absent free hydrochloric acid secretion usually have a definitely lower blood count than those with a normal or nearly normal free hydrochloric acid content.

Only by repeated examination of the blood can this type of anemia be demonstrated. With only an occasional blood

	C.	P.	F.
<i>Breakfast:</i>			
200 Gm. 10 per cent fruit, such as oranges or orange juice, pineapple or pineapple juice, strawberries, or peaches	20		
100 Gm. cooked cereal, such as wheatena, oatmeal, or cream of wheat	10	2.5	1
5 Gm. butter			4.1
15 Gm. (2 slices) whole wheat bread	9	1.5	
120 Gm. cream	6	4	4
3 ounces milk	4.5	3	3
Black coffee			
	49.5	11	12.1
<i>Supplementary Feeding:</i>			
100 Gm. 10 per cent fruit	10	6	6
<i>Luncheon:</i>			
Vegetable soup (60 Gm. 10 per cent vegetables)	4	1	
60 Gm. meat, such as steak, lamb, chicken, lamb chops, roast beef, roast lamb		16	10
90 Gm. 10 per cent vegetables, such as string beans, beets, carrots, onions	6	1.5	
120 Gm. milk or tea			
90 Gm. 5 per cent vegetables, such as asparagus, cabbage, cauliflower, celery, spinach, tomatoes, turnips, lettuce	3	1.5	
5 Gm. butter			8.3
100 Gm. 20 per cent fruit, such as bananas, prunes	40		
15 Gm. whole wheat bread	9	1.5	
	62	20.5	18.3
<i>Mid-afternoon:</i>			
Uncooked vegetable salad			
<i>Supper:</i>			
60 Gm. fish (haddock or salmon)		12	
40-60 Gm. meat, such as lamb, beef, beef steak, chicken		21	12
90 Gm. 15 per cent vegetables, such as lima beans, parsnips, peas	9	3	
90 Gm. 10 per cent vegetables, such as string beans, beets, carrots, onions	6	1.5	
5 Gm. butter			4.1
15 Gm. brown bread	9	1.5	
Lettuce			
150 Gm. 10 per cent fruits	15		
8 ounces milk	12	8	8
	51	46	24.1

(Vegex— $\frac{1}{2}$ to 1 teaspoonful—in milk, hot water, or orange juice should be taken twice a day, preferably with meals.)

NOTE.—The caloric value of this diet is between 2000 and 2500.

well as the iron. The chart (Fig. 120) illustrates the result obtained in a patient in whom a severe anemia of pregnancy was discovered in the sixth month.

Iron has been used by hypodermic injection, either intravenously or subcutaneously, for many years, but in order to give sufficient iron to supply the needs of the organism the dose would be a toxic one and could not be tolerated. Today there is seldom an indication for this form of therapy. The pregnant patient may be suffering from such severe gastric distress that

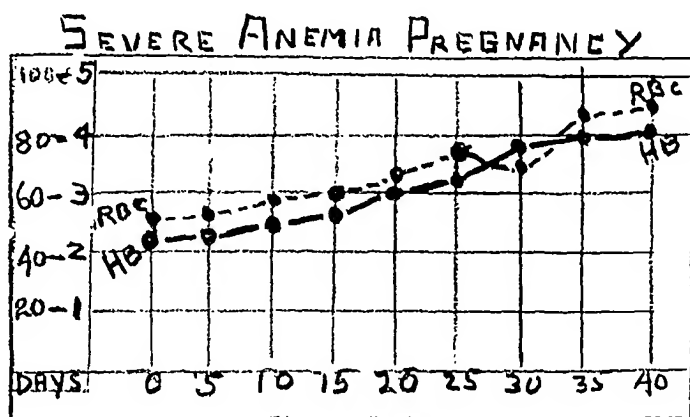


Fig. 120.—Severe anemia of pregnancy. Treatment started in the sixth month. Reduced iron—60 grains daily—resulted in adequate reticulocyte response, and an increase in hemoglobin and red blood cells to nearly normal figures in thirty-five days. The blood count remained normal throughout the remainder of pregnancy. The general improvement in the patient's condition was noticeable. Labor was uneventful.

she is unable to tolerate anything by mouth. In such a condition the hypodermic use of iron might be of some value until the individual is able to take the iron by mouth.

3. SEVERE ANEMIA OF PREGNANCY OF PERNICIOUS TYPE

Fortunately this type of anemia of pregnancy is comparatively rare, if one can believe the reports in the literature. There is no doubt, however, that many of these cases go unrecognized or, if they are recognized, are never reported. If we are on the lookout for this condition, it will be found to be much more com-

count the anemia may not be discovered at an early stage. As soon as the patient reports her pregnancy a complete blood study should be made. If an anemia is present, a blood count should be made every two weeks whether or not adequate treatment is instituted. If no anemia is demonstrable, a blood study should be made at least once a month in order that one may determine the early occurrence of anemia.

It is suggested that the anemia of pregnancy unrecognized or inadequately treated probably plays a large part in the development of pernicious vomiting, premature birth, dental caries, thyroid dysfunction, faulty lactation, delayed involution, lowered resistance to tuberculosis and other infections, post-partum psychosis and possibly toxemia. Certainly unrecognized anemia is a potent factor in the increase of maternal mortality.

As we have already stated, this type of anemia is microcytic or hypochromic. The color index, in spite of its scientific inaccuracy, is a useful clinical aid in differentiating hyper- and hypo-chromic anemia. The volume index is usually less than 1, the iron index is lowered, the white blood cells may be normal or may be increased, and the differential blood count is variable, there being no constant picture. The red blood cells are slightly smaller than normal and show a definite reduction in coloring concentration. The van den Bergh test is usually within normal limits. The fragility, bleeding time, clotting time, and blood platelets are normal.

Treatment.—Diet has already been discussed under the heading of "Simple Anemia" and such a diet is, of course, indicated in this type as well. Iron in adequate dosage is essential. Reduced iron, 30 to 60 grains daily, is usually well tolerated, has a higher content of iron than the iron ammonium citrate, and usually sufficient is absorbed to give the proper hematopoietic stimulation. Because of its heavy weight it can be given in a small capsule which is a distinct advantage. In the cases in which the free hydrochloric acid is low or absent there is better absorption if dilute free hydrochloric acid—15 to 30 minims—or dilute nitrohydrochloric acid—5 to 15 minims—is given as

intravenously or hog's stomach by mouth or autolyzed yeast and normal gastric juice may be used in the treatment of this condition. Any of the forms of liver extract—Lilly's, Mulford's or Valentine's E-29—that are adequate in the treatment of Addisonian or pernicious anemia of the nonpregnant will be found to be efficacious in this disease.

If the powdered extract is used, the dose is 6 ampules daily, given in orange juice, grape juice, broth, or tomato juice. The dose of Valentine's extract, which is liquid, is 3 to 6 tablespoonfuls daily, given in similar media. A reticulocyte count should be made before the treatment is started, and repeated every second day to determine an increase. A blood count is made at the same time, or at three- to five-day intervals.

If the individual is unable to take this extract by mouth, it may be given hypodermically. If the condition is urgent, it may be given intravenously. There are some who prefer the intravenous use of liver extract because one is insured of better utilization than when given by other routes. However, in the great majority of cases it will be found that the intramuscular injection of liver extract is satisfactory. If Lederle's extract is used, the dose is 3 cc. and can be given daily or every other day until an adequate reticulocyte response is obtained. At this time the interval between injections may be increased from two to three days a week, and finally from ten days to three weeks. The extract of hog's stomach will be found to be just as efficacious as liver extract when given by mouth. Some patients prefer this extract to that made from liver. A diet similar to that used in the severe anemia of pregnancy is indicated. The treatment should be continued until the blood count is normal and the patient should be followed after delivery to see that a relapse does not occur. Some of the cases require that treatment be continued for an indefinite period of time.

Blood Transfusion.—Blood transfusions given in small amounts at three- to five-day intervals can bring about, in many cases, an adequate response as quickly, or even more quickly, than that possible through the use of other methods. However, since the advent of liver and extract of hog's stomach transfusion

mon than is supposed. The condition, however, if inadequately treated, carries with it a mortality of 60 to 70 per cent. No doubt many of the cases have been reported elsewhere as cardiorenal vascular disease, just as was the case with the addisonian anemia of the nonpregnant individual.

In considering the etiology of this condition we find it to be practically identical with that of the addisonian type of anemia. There is a deficient or absent free hydrochloric acid content and there is also a lack of the intrinsic factor of Castle in the gastric secretion, differing from the addisonian anemia in this respect—that in most cases the lack or loss of this intrinsic factor is only temporary, while in the majority of cases of addisonian anemia it is permanent. The bone marrow is hyperplastic, megaloblasts fail to mature, the serum bilirubin is usually increased, the liver may be somewhat enlarged, and the spleen may or may not be palpable, and there is a yellowish discoloration of the skin similar to that which we see in the typical addisonian anemia. Nervous phenomena, however, seldom, if ever, occur (cord changes).

The frequent check-up of the blood count is more imperative in this type of anemia because rapid changes may occur frequently. The patient having a 40 per cent hemoglobin one day may be found with 25 or 30 per cent the next. The diagnosis can usually be made by careful blood study. The color index is greater than 1, which indicates that the red cells are more greatly reduced than the hemoglobin. The white cells vary; a leukopenia may be present, but a normal or increased white cell count is more usual. The lymphocytes may be increased, but such a finding is not constant, thereby differing from the typical addisonian anemia. The red cells are larger than normal. The volume index is greater than 1. The fragility of the red blood cells is normal or reduced. The blood platelets are usually somewhat reduced, that is less than 200,000. The bleeding time and clotting time are variables. The quantitative van den Bergh, as already stated, shows an increase. The iron index is normal or greater than normal.

Treatment.—Liver extract by mouth, hypodermically or

similar result was obtained with Mulford's liver extract in twenty-two days.

It is important to emphasize again the necessity for careful observation of all pregnant patients in order to determine the presence of this disease, and, having discovered its presence, that adequate treatment be instituted at once.

is little used in this condition. The indications for its use at the present time should probably be limited to those cases which are critical and in which one hardly dares to wait for the liver or stomach therapy to be effective. In such cases, if the transfusion is in the hands of an experienced man, carefully given after proper cross-matching, there is little danger or reaction and the

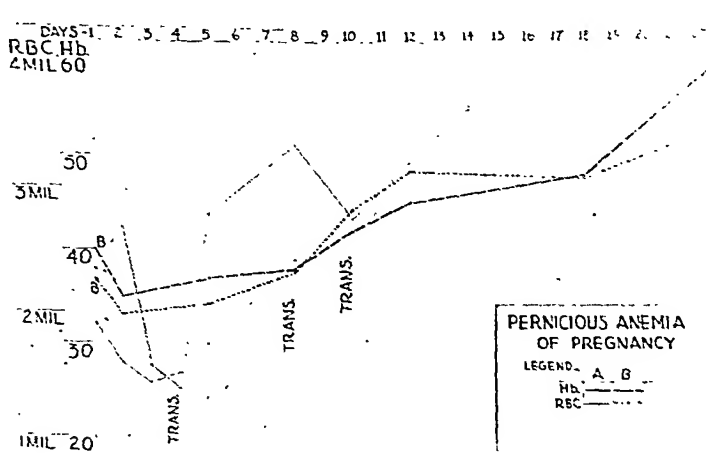


Fig. 121.—Pernicious anemia of pregnancy. During the first pregnancy (A) there was a marked drop in the red blood cells and hemoglobin. On the fourth day after recognition a whole blood transfusion of 400 cc. was administered. Two transfusions of 300 cc. each were given. On the fourteenth day the hemoglobin and red cell condition had reached a safe level. The patient at this point made an uneventful recovery. Five years later, in the second pregnancy (B) the pernicious anemia again developed. The patient was placed on Mulford's liver extract, six ampules daily for one week, and then one ampule three times a day. This resulted in the blood count being brought to safe limits in twenty-three days. No complications occurred and the patient is in good health today.

results will be gratifying. The chart (Fig. 121) demonstrates the results obtained in the same patient in two different pregnancies, in both of which she developed the pernicious anemia of pregnancy which was recognized in one case after birth, and in the second instance in the latter part of the eighth month of pregnancy. The treatment with transfusions brought about a gratifying result in fourteen days, and in the second instance a

the second and 33 in the third. Ebaugh,⁵ in a paper to be quoted in another connection, questioned the professors of medicine in 60 medical schools as to the incidence of psychiatric problems in general medicine and found their answers to average 35 per cent.

From such testimony it is evident that there is a growing general recognition of the importance of emotional factors in illness and that a large part of the practice of every physician consists of patients with an illness of psychogenic origin. In view of these facts it seems extraordinary that until now neither in this country nor abroad have our medical students received any well-grounded or organized instruction in mental functioning and even today far from adequate training is offered.

This subject has just recently been discussed by Ebaugh⁵ in a study of psychiatric education in 60 medical schools in the United States. He found adequate teaching in psychiatry in only 16 of the 60 schools, although he believes that 10 more will soon develop satisfactory courses. Forty per cent of the undergraduate medical students considered their psychiatric training insufficient for their needs.

Psychiatry as still taught in the majority of medical schools is a separate branch of study dealing with diseases of the mind. When the medical student attends the neuropsychiatric division for instruction he is prepared to learn something about a psychotic or "mental" case. When he enters the medical division he turns from psyche to soma and concerns himself with structural or organ disease, frequently forgetting that he is still dealing with a human being. The average intern makes the same error; the patient gets the kind of history that the ward or service requires; if in the gynecological ward a gynecological history, if in the medical ward a medical history, regardless of the nature of the illness. True, if the patient in the medical ward lists a dozen chief complaints and takes up two hours of the intern's time with hair-splitting details of medical history he realizes that he has a "functional case" and that designation both to him and to his older colleagues often carries the connotation "imaginary" or "malingerer." As a result a large number

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PERSONALITY STUDY AND THE PRACTICE OF MEDICINE

PHYSICIANS have always recognized that many patients with physical disease present a "large nervous element." This feature of the illness has, however, largely been considered secondary, and perhaps a consequence of the physical disorder. Psychogenesis has been accepted abstractly with only vague understanding of the nature of mental mechanisms and the part they play in illness. Recent reports, however, indicate that interest in this subject is growing rapidly. Thus Moersch,¹ in an analysis of 500 consecutive patients seen at the Mayo Foundation, reported psychogenic factors of varying degree in 44 per cent; Stevenson,² in a study of 150 patients presenting themselves to a gastro-intestinal clinic, states that there was an important emotional problem in two thirds of the cases; Ziegler,³ in questioning 80 physicians in general practice in New York State as to the percentage of patients consulting them who had no very definite bodily disease as a basis for their complaints, found the answers to strike an average of 19.7 per cent. Reynolds,⁴ in a study of 935 unselected private patients encountered in the practice of internal medicine, concluded that 21 per cent were psychoneurotics. Recently I have studied 100 consecutive private patients classifying them as follows: (1) Those in whom the illness seemed to depend entirely on emotional problems; (2) those in whom the illness seemed in part dependent on emotional problems; and (3) those in whom an emotional problem did not seem to enter into the cause of the illness. Thirty patients were placed in the first group, 37 in

very immature psychosexual development and confirmed the opinion that the sister's marriage had precipitated an invalid reaction in this psychoneurotic individual.

Many members of the medical profession, general practitioners and specialists, too, are treating neurotics and do not know it. It might be remarked that one of the causes of the "prohibitive cost of medical care" is to be found just here. The study of the emotional life of the chronically ill would often obviate the necessity of many of the expensive and time-consuming laboratory investigations.

MEDICINE IN THE MACHINE AGE

The physician of the machine age has a material and structural viewpoint of disease, which has been enhanced by the growing mechanization of medicine.

Zweig describes in "Mental Healers" how the transition from priest-physician and the conception of disease as a visitation from the devil to the structural concept of Virchow led to the separation of disease from the spirituality of man and its disintegration into many separate ailments. Then came the age of specialists to deal with all of these separate ailments. With the specialists came instruments of precision and the mechanization of medicine began. The formula became—cellular disease—structural alteration—mechanical investigation—documentation and standarization of these measured "facts." Rigidity of thought accompanies this rigidity of method and the regimentation of measurements gives a false sense of "scientific" accuracy. What the machine age has failed to recognize is the false premise upon which many of these measurements have been built up. *The disturbance of function, often psychogenic in origin, which in many cases precedes the physical symptoms, has not been recognized.*

With the intensive investigation of organic disease came the equally erroneous method of treating the patient as the "passive" possessor of a diseased organ and assigning to the physician the "active" rôle of removing by one method or another this disease from him. It is not a far cry from the magic

of sick persons are dubbed "damned neurotics" with the unfortunate care that must necessarily follow such a characterization. However, in the hands of many physicians and particularly internists there is a larger group of patients presenting puzzling ailments, not recognized as psychoneurotics, who are exhaustively studied by every conceivable means with the final conclusion by the physician that some obscure cause—infectious, allergic, endocrine or metabolic—is at work, which our modern precision methods of diagnosis have failed to disclose. *He never really concedes that physical disease is not present.* He either cannot or will not comprehend that psychogenic factors are capable of producing the illness.

The patient who undergoes repeated abdominal operations in a vain effort to get rid of pain or discomfort falls into this class. Everyone engaged in hospital practice has seen many such unfortunate individuals.

A young woman at the age of nineteen had her first attack of pain in the right lower quadrant. At twenty the appendix was removed. Six months later she had a pelvic operation because of painful menstruation. At twenty-six she had her third operation for abdominal adhesions. For the next four years she complained more or less constantly and had been in bed for considerable periods because of the pain in the right side. Stricture of the right ureter was suspected but not proved and, finally, after a great deal of hospital investigation a fourth operation was performed in the belief that there was disease of the large bowel, but all organs were found normal.

Here, then, was a patient who had been practically incapacitated for many years and who, during this period of time, had been repeatedly subjected to searching physical investigations and many abdominal operations. What the many physicians attending her had not discovered, or did not know the significance of, was that this long illness began shortly after the fourth of her five sisters married and this patient realized that she would in all likelihood remain a spinster and would then endure a life of drudgery and comparative loneliness. Meek and submissive, unattractive and unintelligent, she unconsciously turned to illness when she found it impossible to compete with her sisters' superiority. Further personality studies disclosed her

been a lack of insight into the emotional problems and accompanying organ dysfunctions of the sick individual for which we have not been sufficiently criticized. It is a curious fact that, although the medical man is constantly confronted with proof that psychological processes influence such physiologic phenomena as blushing, weeping, goose-flesh, the secretion of gastric juice, etc., when he goes one step beyond this to a more than temporary functional alteration of a like nature he either divorces the phenomena entirely from the psyche or assigns to the latter a subsidiary and unimportant rôle.

MENTAL MECHANISMS AND THEIR SIGNIFICANCE IN ILLNESS

Why this should be is not entirely clear. One of the difficulties has been the *lack of knowledge of how to study* the emotional life and an inability to understand the significance of psychogenic factors. To many medical men it is, however, becoming increasingly evident that purely psychic processes are capable of producing physical symptoms which cannot be removed or cured by medicinal, surgical or manipulative means but only by a study directed to the unconscious psychological processes underlying the illness.

Karpman⁷ briefly explains that the mental mechanisms at work are conversion reactions. They take place when an unconscious psychic conflict is converted by the patient into a physical symptom that symbolically expresses the conflict. The patient is not consciously aware of the meaning of this reaction. Behind the whole process is often a desire on the part of the patient to gain a particular point which may be nothing more than a wish for love or sympathy expressed in an infantile manner. In a very brief way this explanation indicates that such mechanisms cannot be adequately understood without some knowledge of unconscious mental processes, and it also tells us that, this being so, any therapy which is conducted entirely on a conscious level must necessarily fail. The following case illustrates some of the points just mentioned.

An attractive young woman of twenty-four, from a small town in another state, came to see me for the first time in September, 1931, because of a slight

of the priest-physician period—*disease is a visitation from without and the doctor exhorts it away.*

In his "History of Medicine" Garrison states that the fundamental error of medieval medical science, as originally pointed out by Guy de Chauliac and elucidated by Allbutt, was in the divorce of medicine from surgery. He might have added that the fundamental error of medical science in the twentieth century is the divorce of psychiatry from medicine and surgery.

One cannot speak of Allbutt's name without calling attention to his courageous efforts in behalf of the neurotic patient. But, just as the medical world took more than a quarter of a century to assimilate his teachings on hypertension and vascular disease, so have we failed to learn completely another important lesson to which, with trenchant pen, he called attention almost fifty years ago. Speaking of the visceral neuroses⁶ he said: "A neuralgic woman seems thus to be peculiarly unfortunate. However bitter and repeated may be her visceral neuralgias, she is either told she is hysterical or that it is all uterus. In the first place she is comparatively fortunate, for she is only slighted; in the second case she is entangled in the net of the gynecologist, who finds her uterus, like her nose, is a little on one side, or again, like that organ, is running a little, or it is as flabby as her biceps, so that the unhappy viscus is impaled upon a stem, or perched upon a prop, or is painted with carbolic acid every week in the year except during the long vacation when the gynecologist is grouse-shooting, or salmon-catching, or leading the fashion in the Upper Engadine. Her mind thus fastened to a more or less nasty mystery becomes newly apprehensive and physically introspective and the morbid chains are riveted more strongly than ever. Arraign the uterus, and you fix in the woman the arrow of hypochondria, it may be for life."

The unfortunate position of modern clinical medicine has come about because of the somatic and physiologic orientation of the physician to the exclusion of adequate training in medical psychology. It must be admitted that tremendous progress has resulted during this period of laboratory ascendancy but, because of the absolute neglect of psychogenic factors, there has

This case is cited to illustrate the interrelation of psychic and somatic spheres and not as a model of psychotherapeutic management. There are grave dangers ahead in the necessary adjustments of married life for such an emotionally immature person. Fremont-Smith⁸ recently briefly explained how such problems date back in their beginnings to the very early days of childhood.*

Such a person's childhood training is often unfortunate. Parents frequently try to realize their own unfulfilled ambitions in their children. Frustrated themselves they seek satisfaction in their children's successes. Children of such parents are often made the center of attention and begin to enjoy this superiority above all else and make every effort to hold it. When a brother or sister comes along they are fiercely jealous and do anything to command attention. When these children first enter school they are unhappy. They miss home where they are the central figures and, *symptoms coming to the rescue*, they succeed in regaining this friendly atmosphere. People speak of them as being "too sensitive" for school. They are shy and take responsibilities overhard. Because they never learn to accept inferiority, to fail courageously, they live in a constant fear of failure. To be at peace with themselves they must excell. They grow to demand not only superiority as their goal in life but absolute perfection. As they grow older and the avoidance of mistakes becomes increasingly difficult they restrict their world to those who look upon them with special consideration. They play by themselves rather than with others. They grow up without the training for marriage which should result from the normal attractions toward the opposite sex. Steeped in romance through their reading and daydreams, with considerable aid from the movies, the realities of marriage constitute a supreme danger for such individuals. Sensing their own inadequacies they nevertheless look for perfection in others and failing to find it they make every effort, usually wholly unconsciously, to escape from mar-

* Some of the material from the succeeding paragraph has been taken from his excellent article but no attempt has been made to preserve the exact language of the author.

continued fever and a suspicion of pulmonary tuberculosis. The fever was discovered in October, 1930. She gave up her work and was treated as a case of incipient tuberculosis because her doctor discovered "something suspicious in her lung." She had then consulted a lung specialist who examined her thoroughly and then told her that he did not *think* that she had tuberculosis. Nevertheless her fever continued and she remained at rest until she consulted me one year later. She had slight disturbance of the bowel, that is, constipation with occasional slight diarrhea and a good deal of mucus in the movements.

Physical examination and x-ray failed to disclose evidence of organic disease, and discussion brought out the following story.

During the winter of 1929-30 she was keeping company with a young man and the townspeople took it for granted that they were engaged. During the following summer while she was considering the question of the marriage date she became irritable, lost weight and felt ill. In September she had what she calls "an attack of ptomaine poisoning" following a dietary indiscretion. It was during this attack that the fever was discovered and was apparently not ascribed to her bowel disturbance but rather to the lung. She then quit work and spent practically a year in bed. During this period the young man remained as attentive as ever but she told herself that it was not fair to him to continue her engagement. She argued with herself in the following fashion: That in view of her continued illness she felt it must be better to give him up; that she would not be strong enough to marry, to have children or to do house work. She had many more "reasons" why she should not marry. For one thing a brother and sister both had been unhappily married and were divorced. She also felt that her mother needed her, that she was happy at home and did not like to leave. She informed me that her husband-to-be did not have enough money to marry but, on further discussion, there seemed no question that he could adequately support her.

The proper approach to this problem seemed to me to be exactly the opposite of her previous physicians who had agreed with her that she must exercise caution and that it would be better for her to put marriage out of her mind "until she was well." I told her that there was no physical evidence to indicate organic disease; that her slight fever was due not to any lung trouble but simply to a mild mucous colitis which in turn was very closely associated with the worry and stress incident to the problem of marriage. Then I told her that her illness represented an unconscious effort on her part to escape the responsibilities of marriage, and that all the points she raised about not getting married were simply self-deceptive rationalizations to assist her in escaping this responsibility. After accepting this statement she admitted that shortly after she became engaged "she had a premonition that she would get sick." I told her that it was necessary for her to face the fact that she must either marry or not marry but that she could not go on as at present. Shortly after that she announced to me that she would determine upon a marriage date. Following this resolution she became worse than ever. Her menses became irregular, she was fatigued all of the time, had pain in the back and became upset if there was any variation from her usual routine. Finally, she forced herself to marry in February, 1932, and twice since, the last time in April, 1933, I heard that she was very well.

tinctive features to be discovered only by personality study. *The diagnosis of "functional disease" or neurosis must be established not simply by exclusion but by its own characteristics.* Personality study is just as important in the study of chronic illness as laboratory investigations and the technic can be acquired just as definitely.

With such errors in diagnosis are associated expensive and time-consuming investigations, unnecessary operations, and a degree of pathetic helplessness not to be encountered elsewhere in medicine. No field of medicine is free from such errors and in certain specialities they very often occur. This is particularly true of gastro-enterology because the gastro-intestinal tract is so intimately concerned in the instinctual development of the infant and thus habit patterns are laid down which later accurately reflect the emotional state.

Still another problem enters into the diagnosis and care of neurotic patients. The physician is often placed in a special predicament with regard to them for if he successfully removes a symptom the patient may shortly present something worse. He is simply displacing a source of unconscious gratification. As Meninnger in "The Human Mind" has stated, "Hell hath no fury like a woman scorned except a neurotic from whom you remove a pet symptom," and many a psychiatrist has testified to the fact that a conversion symptom may be the least dangerous type of symptom for a neurotic to assume.

Numerous cases have been cited in which following shortly upon the removal of such a symptom, a severe neurosis or even a psychosis makes its appearance. This is particularly important to the surgeon who must know more about the psychological preparation of his patient for operation. A slight operation in a patient not recognized as potentially neurotic will sometimes lead to a more severe illness and an extreme degree of invalidism.

Thus a young woman was subjected to a lumbar puncture in the course of a complete examination to find the cause of frequent headaches. Immediately she became ill with more severe headache, pain in the back and various bowel disturbances and remained bedridden for nine months. This was her infantile

riage. Very often, as in the case just cited, an illness comes to the rescue—as long as they are ill they cannot marry.

When they do succeed in forcing themselves to marry they go through a difficult period of adjustment, and illness again may come to the rescue. Digestive and bowel disturbances, symptoms simulating heart disease, and so-called “inward troubles” are some of the illnesses that aid them in escaping the responsibilities of marriage and may take them home again to mother. When children come to them the whole vicious process is repeated—the unsatisfactory marriage relationship makes them seek emotional satisfaction in their children and the indulgent mother or stern father again sows the seed for another spoiled life. Eben Holden said of the man and his horse, “Got t’ judge the owner as well as the hoss and if there’s anything the matter with his conscience it’ll come out in the hoss somewhere.” The same thing is true of parents and children. If the parents have a disturbance in their emotional lives it is almost certain to show up as some defect in the personality of the child.

Marriage problems are a fertile source of emotional tension giving rise to physical ailments. This in itself would form a very interesting discussion. Doctors repeatedly advise men and women to marry, seeking in this fashion a short cut to the settlement of their emotional problems. What the doctor often does not realize is that these emotionally immature persons are incapable of accomplishing the hurdle of marriage.

THE DIAGNOSIS OF NEUROSIS

The organic training of the physician leads him to believe that by paying too much attention to psychogenic factors he may make grave errors in diagnosis by overlooking organic disease. This, of course, is possible, but how much more frequent is the opposite mistake, that is, missing the diagnosis of neurosis and treating the patient as organically diseased. This happens most frequently because modern clinical medicine attempts to establish the diagnosis of “functional disease” by ruling out organic disease through medical history, physical examination and laboratory investigation. But neurosis has its own dis-

their students in medical psychology and physicians are forced to depend upon their own unsystematic study and observation. As a consequence they are unfamiliar with a growing and scientifically established body of knowledge concerning personality study and its value from the standpoint of ill health.

To paraphrase Sullivan,⁹ *when medical training is made to include precise information about psychogenic forces in disease then and only then will the physician be adequately trained for the management of ill people.* Instead of giving medical or surgical treatment for a psychogenically determined complaint he will make an exact diagnosis not simply by eliminating organic disease but by thoroughly investigating the personality of his patient, for which he will have as much respect as the physician of today has for vaccines and blood chemistry.

Then he will truly study the organism-as-a-whole to which concept today only lip service is paid.

His aim must then be to rid the individual of the need for symptom formation, and this can only be achieved by a reconstruction of the patient's emotional life. For this purpose his treatment must be based upon a knowledge of the psychological processes underlying the illness.

Medicine faces a new era—a new frontier. During the past century it attacked frontiers in pathology, in bacteriology and in chemistry. In the twentieth century it faces the frontier of psychology and here the same important additions to the large body of medical knowledge are to be made.

From Virchow who said in the course of a congress at Rome, "There are no general diseases. From now on, we shall recognize only diseases of organs and cells," we have come almost full circle in beginning to understand that *there are no diseases of organs and cells.* Disease, as Draper¹⁰ suggests, is a *psychosomatic reaction—a disorder of the organism-as-a-whole.*

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way of expressing disapproval of her brother's marriage—her only brother to whom she was closely attached and who acted in the capacity of father to the family. The slight operation acted as precipitating agent and inadequate psychological understanding on the part of the physician permitted the illness to continue. She recovered when the meaning of the illness was made clear to her and shortly afterward she successfully married an older man.

Another error in diagnosis is in the recognition of "a nervous element" but ascribing it to a structural alteration which may have nothing to do with the psychogenic basis of the illness. The physician must always ask himself: *Are the organic defects revealed by the physical examination sufficient to explain all of the symptoms?* Too often, I fear, he makes the clinical picture fit the defects, and ascribes the illness to a discoverable abnormality.

A single woman of twenty-nine had curious sensations in the head, irregular menses, and spells of weakness and trembling. Physical examination disclosed pronounced evidence of a mitral valvular defect which was thought to be the basis of her illness. But personality study showed marked unconscious homosexual strivings which had interfered with her arrival at a heterosexual goal and this was manifested consciously by a pronounced masculine protest. She was forever being disappointed in her female friends and fighting with her male employers.

The unconscious psychogenic material indicated that her chief symptoms were related to her deeper fears and anxiety. The unconscious homosexuality constituted a threat to her personality which was responsible for her inner insecurity. As far as her physical health was concerned the valvular defect could for the time at least be practically disregarded.

The skeptical will say "but all people have emotional difficulties; why are we not all ill." What determines whether emotional factors will produce illness and in what part of the body (or personality) that illness will manifest itself is a yet largely unexplored field. All persons are exposed to germs and yet few are infected, and in a similar fashion all are exposed to emotional factors but only those marked out by aberration of personality development will fall prey to neurotic disorder.

ORGANISM-AS-A-WHOLE CONCEPT

In spite of the great importance of psychogenic factors in illness the majority of medical schools do not adequately train

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commonly occur. This clinical picture is one of coronary thrombosis and the majority of signs and symptoms also fit into the description of the clinical picture present in ruptured peptic ulcer, acute pancreatitis, an attack of cholelithiasis, acute intestinal obstruction and acute appendicitis.

The time-worn diagnosis of acute indigestion, ending in sudden death or occurring within four weeks following the attack and not considered seriously, is no longer excusable in the light of our present-day knowledge of acute coronary occlusion. Many cases of acute coronary occlusion, even though not operated upon, and casually diagnosed as acute indigestion, can be restored to health if they were kept in bed for four to six weeks, this being part of the proper treatment in conjunction with routine therapy.

History.—The past history, carefully elicited from a patient is important and useful in arriving at a correct diagnosis between these two grave conditions. Cardiovascular disease as a cause of death in the family history may be confirmative evidence.

The presence of a mild glycosuria or a well-developed diabetic condition in a patient should suggest the need of careful examination of the cardiovascular system. A history of cardiac pain, of angina brought on by effort, walking against a heavy wind, or emotional disturbances should arouse the suspicions as to the possibility of the so-called "acute surgical abdomen" being coronary thrombosis.

Hypertension.—The presence of hypertension or, in its absence, sclerosis of the retinal vessels is often an antecedent finding of coronary thrombosis. A previous history of disease of the heart with or without the presence of an arrhythmia is important in directing particular attention to the heart as a possible seat of the pain.

Pain.—Although coronary thrombosis occurs in a number of cases without previous attacks of substernal distress, pain or discomfort, this is not the rule. A careful and thorough questioning frequently reveals the history of previous paroxysms of substernal pain of short duration radiating down one or both

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CORONARY THROMBOSIS SIMULATING AN ACUTE SURGICAL ABDOMEN. REPORT OF TWO CASES

THE recognition of coronary thrombosis by a group of signs and symptoms is relatively easy in a typical case. Occasionally other disorders occurring in the thorax may offer difficulties in the diagnosis of this condition. In addition, coronary thrombosis with abdominal symptoms and signs may so obscure the clinical picture that the real lesion may be unrecognized, especially if not kept in mind.

The purpose of this discussion is not to describe additional cases of acute coronary occlusion, already so well done in literature during the past decade, but to further emphasize the fact that the clinical picture of coronary thrombosis may closely resemble an acute surgical abdomen and the points to be considered in the differential diagnosis.

A surgical operation performed upon a patient suffering from coronary thrombosis incorrectly diagnosed as an acute surgical abdomen, carries with it a greater risk due to the additional strain placed on an already acutely damaged heart.

The pain of coronary thrombosis is sudden in onset accompanied by shock, often is located in the lower sternal or upper abdomen and usually is continuous up to a period of twenty-four hours, even if sufficient morphine sulphate is given hypodermatically to afford some relief.

Vomiting, marked rigidity of the abdominal muscles in some cases, accompanied by tenderness in the epigastrium, may direct attention to the abdomen more than to the heart.

The liver often becomes palpable and jaundice is present. Within twenty-four hours after the onset, fever and leukocytosis

the systolic pressure falls suddenly following the coronary thrombosis, often below 100 mm. Hg. In the acute surgical abdomen it does not fall as suddenly and then only if profound shock is present.

Pericarditis.—The presence of a to-and-fro grating sound frequently heard over the heart, within twenty-four to forty-eight hours, is diagnostic of a cardiac accident rather than of an acute surgical abdominal condition. Unexplained cases of acute pericarditis in the past with abdominal symptoms unquestionably have been instances of acute coronary occlusion primarily. This sign should be sought for at frequent intervals during the period of pain, because of its transitory nature.

Heart Sounds and Radial Pulse.—Although the heart may be normal in rate and rhythm in a few cases the predominant finding is that the heart sounds are weak and poorly heard. They are frequently rapid, although not uniformly so. The rate may be normal or slower due to the presence of heart block. Often an arrhythmia develops very soon after the onset of substernal pain.

This arrhythmia may be due to auricular fibrillation, paroxysmal ventricular tachycardia, auricular flutter, heart block and premature contractions. It may become evident also immediately following the attack, to disappear within a week or to become permanent, depending on the type. The radial pulse may, in addition to being influenced by the arrhythmias, be small and almost imperceptible due to low blood pressure. Gallop rhythm is of very frequent occurrence in severe attacks of coronary thrombosis and not so in an uncomplicated acute surgical abdomen.

Liver.—The liver may be palpable with the onset of substernal and epigastric pain or be enlarged due to congestive heart failure or to cholelithiasis with colic. Jaundice may be a sign found in both conditions so that its presence does not help greatly in the differential diagnosis of these two conditions.

The Electrocardiogram.—Among some of the more common changes in the electrocardiogram are the diminution of the amplitudes of the various curves, the high take off of the T wave

arms, transient in character and relieved by the nitrites. These attacks are readily diagnosed as angina pectoris. It is common knowledge that coronary thrombosis frequently occurs in cases of angina in a severe if not a fatal form.

The location of the pain or distress in coronary thrombosis if epigastric also is usually substernal to a certain degree. The pain of an acute surgical abdomen is rarely entirely substernal. The pain due to coronary thrombosis is described as choking, oppressive, a suffocating or a viselike sensation such as in gallstone colic. The coronary pain, if accompanied by rigidity of the upper abdominal muscles, is rarely associated with distention of the abdomen and not with obliteration of liver dulness.

Dyspnea.—This symptom in a few cases may be the most prominent one with little if any substernal pain and its presence strongly suggests cardiac involvement, and especially so if Cheyne-Stokes type of breathing is present. A history of dyspnea on effort, prior to the occurrence of pain in lower sternum and upper abdomen is strong evidence in favor of the condition being cardiac in origin.

Cyanosis.—The slightest degree of cyanosis is an evidence of anoxemia or ischemia of the myocardium and is invariably absent in an acute surgical abdomen.

Fever.—Following the condition of shock, which is present in both coronary thrombosis and severe acute surgical abdomens, fever appears. The temperature by mouth early is usually subnormal in both conditions. If taken by rectum, fever rising more rapidly and usually to higher levels, occurs more frequently in an acute surgical condition (except in stone colic) than in coronary thrombosis and early may become septic in type.

Leukocytosis.—The leukocyte count in acute surgical abdomen, except in gallstone colic, usually rises higher, on an average 20,000 to 25,000, than in acute coronary occlusion 10,000 to 15,000 with the polynuclears predominating in both conditions.

Blood Pressure.—The knowledge of the blood pressure readings which have been taken prior to the onset of substernal or abdominal pain is most desirable because in a number of cases



Fig. 122.

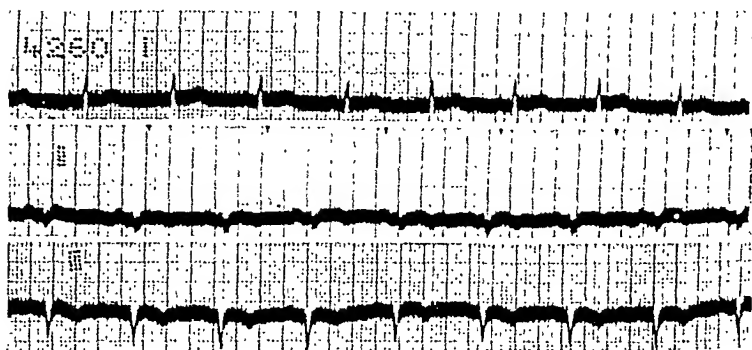


Fig. 123.

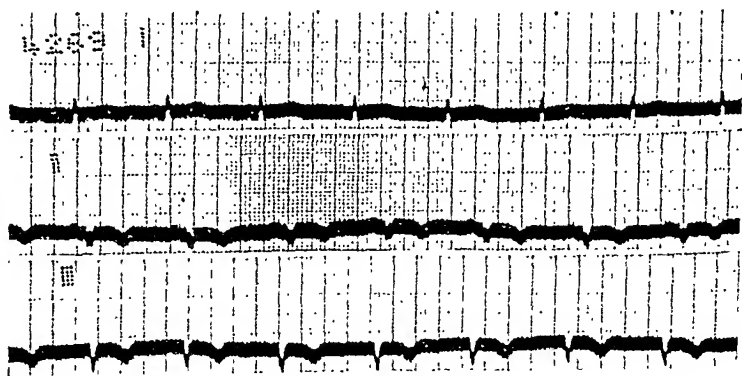


Fig. 124.

from the downstroke of the R wave and the complete inversion of the T waves in leads Nos. I and II or both. Other variations in the electrocardiogram have been present in a smaller number of cases of acute coronary occlusion, but are not solely characteristic of this condition, being also found in other degenerative changes in the myocardium. The prominent Q wave in lead No. III is strongly suggestive of acute coronary occlusion. These variations in the electrocardiogram may be present within several hours after the attack and change in form from day to day.

Case I.—Mrs. C., aged sixty, a woman school-teacher suffered an upper abdominal and lower sternal colicky pain, as she was dismissing her class for the day. This pain was sufficiently severe to cause her to fall and go into a state of shock. She was immediately taken to the hospital. There a history was obtained of numerous slight previous attacks, lower sternal and epigastric distress, believed by her to be indigestion and never severe enough to consult a physician. Otherwise she enjoyed the best of health throughout her life.

Physical Examination.—On admission to the hospital she was slightly jaundiced, pallor was present and she was in a state of shock. She had some dyspnea. The examination of the lungs did not reveal the presence of any râles. The heart was enlarged to the left of the midclavicular line by $\frac{1}{2}$ inch in the fifth interspace. Sounds were distant and poorly heard. The pulse rate was 76 per minute and regular. Blood pressure 90/60. There was no previous record for comparison.

The muscles of the upper right quadrant and epigastrium were rigid and tenderness was present over the entire abdomen. The liver was not palpable. Nausea and vomiting of stomach contents, containing considerable amount of bile, continued at intervals for three hours.

The leukocyte count was 12,000. In view of previous attacks of distress complained of, which was located in the upper epigastrium and lower substernal region, more or less continuous in spite of jaundice a diagnosis of acute coronary occlusion was made.

The basis for making the diagnosis was a history of distress both epigastric and substernal. The pain she described as colicky is the exception in an attack of coronary thrombosis, in which the pain is usually continuous in character.

An electrocardiogram with low amplitude of all complexes in leads Nos. I and II was obtained. Subsequent x-ray examination of the gallbladder revealed nothing abnormal.

After six weeks in bed she recovered and three months later returned to her school work, symptom-free. While dressing one morning two years later, suddenly she suffered another attack of a similar nature which ended fatally, sixteen hours after the onset.

Case II.—Mr. A. B., aged sixty-seven, was brought to the hospital in a state of shock, on June 27, 1932. He gave a history of having eaten cantaloupe for

breakfast which had disturbed his digestion resulting in nausea, vomiting and syncope, during the act of climbing the stairs going to his office about one hour after the morning meal. He was examined thirty minutes after the onset of the pain, which was located in the lower substernal region and epigastrium.

Physical Examination.—The patient was deeply shocked, the skin was moist and the color was pale with a cyanotic background. The lungs were clear and resonant throughout. The heart was enlarged 1 inch to the left of the mid-clavicular line in the fifth interspace. The sounds occurred irregularly and were moderately well heard, unaccompanied by murmurs.

His blood pressure was 120/80. The temperature was 97.3 F. by mouth. The pulse rate was 76 per minute and irregular.

The muscles of the abdomen were rigid to the point of bearing the full force of a heavy palpating hand. Definite but not marked tenderness in the epigastrium was present. Mentally he seemed confused, almost from the beginning of the attack. He was writhing in continuous pain.

He always had enjoyed excellent health and the attacks he believed to be indigestion, suffered previously to this severe one were no doubt mild attacks of coronary artery disease. The leukocyte count soon after admission was 10,500.

The electrocardiogram (Fig. 122) was made within one hour after onset and was of great assistance in making the correct diagnosis. The changes were diagnostic of coronary thrombosis.

Another electrocardiogram (Fig. 123) was made five days later and indicates how rapidly changes take place in the curves. Figure 124, made twelve days later than Fig. 123, records a less degree of change in the curves than in the first five days between Figs. 122 and 123.

Conclusions.—The clinical picture of an attack of coronary thrombosis severe enough to simulate the actual surgical abdomen is described.

The abstracts of 2 case histories are presented for the purpose of emphasizing the important points of the similarity in the two conditions.

The history of previous attacks of angina pectoris or mild seizures of substernal pain distress with or without signs and symptoms of cardiac insufficiency, except under more than ordinary effort, but with those findings described here, present in coronary occlusion should help in making the differential diagnosis of these two conditions.

The electrocardiogram in a number of cases can be very useful in helping differentiate an attack of coronary thrombosis simulating an acute surgical abdomen when considered in connection with other findings present.

lesion in the base of the lung, in the presence of a normal apex, should be considered as nontuberculous unless tubercle bacilli are found in the sputum or the roentgenogram indicates a shadow which is characteristically tuberculous in type. Landis⁷ states that primary basal tuberculosis is rarely found. He has not discovered a case at postmortem. Kidd⁸ in England gives the proportion of basal to the apical form as one to five hundred. Sir William Osler⁹ reported that his series indicated a higher percentage. Louis¹⁰ in France discovered 2 in 123 cases. In the United States Rosenblatt¹¹ found 3 in 1000 cases; Middleton¹² discovered six in a search lasting for six months; Dufault¹³ found 1 case in a sanatorium of 365 beds; Dunham and Norton¹⁴ reported 26 cases admitted to a 250-bed hospital during a period of two years. Ross¹⁵ in Canada discovered 11 cases among 60 tuberculous nurses. In a series of 500 consecutive cases admitted to the Department for Diseases of the Chest, Jefferson Hospital since 1928, 5 were diagnosed as basal pulmonary tuberculosis.

The following cases are presented because certain manifestations are not unlike those in nonspecific pulmonary infections. Diagnosis was not established in two cases until after an extensive search had been made.

Case I.—L. G., a white male painter, aged twenty-seven, was admitted on January 17, 1928, complaining of cough, expectoration (100 to 150 cc.), night-sweats and loss of weight. The past history is irrelevant except for a question of inhalation of a foreign body in 1924. The present illness began in 1925 with an attack of hemoptysis. A productive cough followed in one month. A tentative diagnosis of pulmonary suppuration due to a nonopaque foreign body was made. His symptoms disappeared following a period of rest in bed. In December, 1925, he had pain in the right lower axilla, elevation of temperature in the afternoon, cough and expectoration. He lost 8 pounds in weight (the highest weight was 140 pounds in 1918). Physical examination was essentially negative except for slight clubbing of the fingers and the chest which showed an increase in the anterior posterior diameters, limited expansion of the lower right side and over this area increased vocal fremitus, dull percussion note and prolonged, harsh breath sounds and coarse râles. The patient was fairly well nourished. The afternoon temperature on admission was 100 F. The pulse was 90, the respiratory rate was 20. Two days following entry, while at rest in bed, the temperature returned to normal where it remained. Urinalysis and blood counts were essentially normal. Numerous tubercle bacilli were found in the sputum. The roentgenogram of the

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BASAL PULMONARY TUBERCULOSIS*

SINCE Laënnec's¹ classical description of pulmonary tuberculosis and the later writings of Fowler² the apex of the lung has been recognized as the site of first parenchymal activity. So generally has this been accepted that the incidence of primary basal involvement is regarded as of extremely rare occurrence. However, the acceptance of this view has not been without discussion, especially in recent years since roentgenography and bronchoscopy have thrown considerable light on basal processes of unknown etiology.

That no question was raised as to the infrequency of primary basal tuberculosis of the lungs is shown in the writings of Laënnec¹ when he stated, "It is extremely rare for the excavation to be first developed in the middle or the base of the lungs." Stokes³ taught also that "simple bronchitis is seldom circumscribed, while that of the consumptive is commonly so; the latter begins in the upper portion of the lung, remains obstinately fixed in the air tubes, gradually spreads downward. Tuberculous ulceration may be intense in the upper lobe while the lower is altogether free. . . ." Fagge⁴ believed "it never happens that the tuberculous process spreads upward from the base of the lung into and through the upper lobe. What has sometimes been called basal phthisis is a distinct affection which has been described under the name of chronic pneumonia." Funk⁵ taught it is a good rule to remember that the primary basal lesion is rarely tuberculous. Fishberg⁶ concludes that a

* From the Medical Service of Dr. Thomas McCrae and the Department for Diseases of the Chest.

first year. All symptoms have disappeared. She gained from 147 to 181 pounds in weight.

It appears in this patient that the early pulmonary manifestations were tuberculous in origin. However, a similar picture has been noted in nonspecific pulmonary infections and may follow lobar pneumonia, although less frequently than previously supposed. Because of the history it was necessary to consider pneumonia with subsequent change in the structure of the lung as an etiologic factor. The case emphasizes the importance, as in Case I, of the need for careful sputum examinations. These should be carried out in every patient who has pulmonary symptoms lasting for more than six weeks. In patients who raise sputum with difficulty satisfactory specimens may be obtained following the administration of 5 drops of a saturated solution of potassium iodide every four hours for six to eight doses.

Case III.—G. W., a white housewife, aged thirty-one, was admitted on September 20, 1932, complaining of cough, expectoration, weakness and loss of weight. The past history was irrelevant except that a brother died of tuberculosis at the age of thirty-five, and that she has had frequent upper respiratory tract infections. The present illness began in February, 1932, when she had a severe "chest" cold. A "dry cough" lasted for one month, became productive and later decidedly mucopurulent.

Physical Examination.—This was essentially negative except that the expansion of the chest was slightly limited below the right axilla. Over the right base the percussio note was dull, the breath sounds were tubular in quality and numerous crackling and coarse râles were heard. The patient was well nourished. On May 19, 1932, the x-ray examination showed no definite evidence of unhealed pulmonary tuberculosis but there was a definite increase in the lung markings in the right cardiophrenic angle which was suggestive of bronchiectasis. The urinalysis, blood count, the blood Wassermann and Kahn reactions were negative. In nine sputum examinations no tubercle bacilli were seen. The temperature varied between 98.3 and 99.2 F.; the pulse rate between 80 and 100 per minute; the respiratory rate was normal. Bronchoscopy was being considered when on the tenth sputum examination tubercle bacilli were found. On October 1, 1932, artificial pneumothorax treatments were started. The collapse of the apex of the lung was satisfactory but the basal area was held out by adhesions. Cough and expectoration continued and tubercle bacilli in large numbers were found in the sputum. On October 30, 1932, the phrenic nerve was crushed by Dr. J. B. Flick. The artificial pneumothorax treatments were continued. At present the diaphragm is elevated and the collapse of the entire lung is satisfactory. It appears the elevated diaphragm shifted the base of the lung medially as the pressure of the artificial pneumothorax forced the base downward and toward the medi-

lungs showed a cavity in the lower lobe of the right lung and increased density in the adjacent areas. The picture was not unlike that seen in pulmonary abscess. His condition improved and he signed a release from the hospital on the forty-sixth day after entry.

The history of inhalation of a foreign body, signs of a basal pulmonary lesion and clubbing of the fingers suggested a diagnosis of pulmonary suppuration. The finding of tubercle bacilli in the sputum, however, pointed to pulmonary tuberculosis as the underlying condition and suggested that the foreign body, if inhaled, as stated in the history, was perhaps incidental. The clubbing of the fingers could be explained on the basis of associated bronchiectasis which has been noted in tuberculosis as well as in suppurative processes. The shadows on the roentgenogram were quite characteristic of cavity formation in lung abscess and could not be differentiated from early excavation in pulmonary tuberculosis. The case emphasizes the importance of careful examination of the sputum. The problem would have been confusing without information derived from this procedure.

Case II.—C. McC., a white female stenographer, aged twenty-six, was admitted on September 21, 1929, complaining of cough, blood-streaked sputum, loss of strength and weight. The family and past histories were essentially negative. The present illness began in October, 1928, when she had a severe cold in the chest. In December, 1928, elevation of temperature and pain in the region of the left scapula occurred and a diagnosis of pneumonia was made. She remained in bed for four weeks and her temperature returned to normal. Her health was good until August, 1929, when the pulmonary symptoms returned.

Physical Examination.—This was essentially negative except that expansion of the chest was limited in the lower half on the right side. At the base of the right lung the vocal fremitus was increased, the percussion note was impaired and over this area the breath sounds were tubular in quality and a few crackling râles were heard. There was slight clubbing of the fingers. The patient was well nourished. The roentgenographic study by Dr. John T. Farrel, Jr., showed an extensive process in the lower half of the right lung with a cavity at the level of the eighth rib posteriorly. Throughout the lower half of the left lung there was a considerable increase in the markings. The upper lobes of both lungs were clear. Urinalysis and blood Wassermann and Kahn reactions were negative. The blood count showed slight secondary anemia. Tubercle bacilli were found in three sputum examinations. The temperature varied between 98.2 and 99.3 F., the pulse rate was 90 to 100 per minute and the respiratory rate 20. The patient remained in bed for six months. She received artificial pneumothorax treatments for two years. The cavity was not seen in the roentgenogram after the

order to obtain a more satisfactory collapse Dr. John B. Flick crushed the phrenic nerve. Following this the cavity wall showed definite closure and a decrease in cough and expectoration occurred. (See illustrations.)

In this case the striking similarity of signs and symptoms between basal pulmonary abscess (resulting from nonspecific infection) and basal tuberculosis should be noted. The diag-

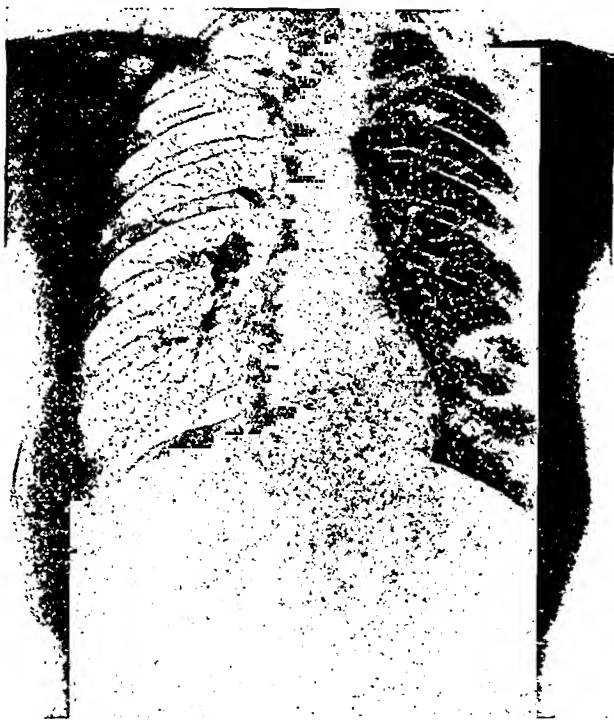


Fig. 125.—A roentgenogram showing a cavity at the level of the eighth rib before collapse of the lung.

nosis would have been uncertain without bronchoscopy. The failure to obtain tubercle bacilli in routine examination is not clear because it is known that tuberculous cavities are rich in bacilli. It is possible that excavations in basal tuberculosis are less "open" than apical cavities, and that obstructions in the bronchi may interfere with free evacuation of the contents. The effects of treatment in this case are interesting and emphasize the value that may be obtained in utilizing certain physiologic

astinum. Cough and expectoration have subsided and the temperature has returned to normal.

The history of frequent upper respiratory tract infections, the increased tissue detail in the lower fields of the right lung and the clinical findings suggested strongly the possibility of bronchiectasis. However the question raised repeatedly during the examinations was the significance of a unilateral basal pulmonary lesion with no history of foreign body or pneumonia which could explain a localized process. It was emphasized that an upper respiratory tract infection usually causes bilateral bronchiectasis. The problem was settled in discovering tubercle bacilli in the sputum. If this had not occurred bronchoscopy would have been indicated in order to obtain secretions for special study and to inject lipiodol into the bronchi for mapping of the lower bronchial tree.

Case IV.—L. E., a white nurse, aged forty, entered on February 13, 1933, complaining of cough, expectoration (150 to 200 cc.), loss of weight and strength. The family and past histories were essentially negative. The present illness began with malaise in June, 1932. Her symptoms were marked six months ago when she stopped work because of weakness. She returned to work improved after one month. In January her cough returned and she expectorated daily about 1 glassful of fetid mucopurulent sputum.

Physical Examination.—This was essentially negative except that the respiratory expansion of the chest was limited below the left axilla. Over the base of the left lung the percussion note was dull and distant tubular breath sounds and crackling râles were heard. The roentgen-ray examination by Dr. John T. Farrell, Jr., on February 13, 1933, showed a large cavity containing a small amount of fluid in the lower portion of the left lung. There was comparatively little tissue change surrounding the wall of the cavity. The urinalysis, blood count, blood Wassermann and Kahn tests were negative. No tubercle bacilli were found in the sputum. On February 13, 1933, a bronchoscopy was performed by Dr. Louis H. Clerf. This showed a moderate amount of pus coming from the posterior subdivision of the left lower lobe bronchus. There was a marked inflammatory reaction of the bronchial mucosa with formation of granulation tissue. The secretion was examined for tubercle bacilli but none were seen. Two further bronchoscopic examinations were made and the secretions studied microscopically but no bacilli were found. Cultures were obtained and after three weeks tubercle bacilli were discovered by Dr. C. J. Bucher. Subsequent examinations of the sputum showed bacilli on ten occasions. Artificial pneumothorax treatments were started in order to compress the left lung. The upper lobe collapsed and the cavity was shifted downward and toward the mediastinum. Although the patient's general condition improved, cough and expectoration continued. In

is highly desirable if there is any question of possible "blocking" of secretions which in the presence of associated abscess or bronchiectasis may be harmful. The advantages are obvious in realizing that regeneration of the crushed nerve occurs usually within six months whereas the cut nerve may not be reunited for a much longer period. The occurrence of gastro-intestinal symptoms following elevation of the diaphragm on the left side may be a further reason for desiring the return of normal excursions. This, apart from any permanent tissue change in the diaphragm such as atrophy, stretching and thinning of the wall due to disuse and trophic influences may be an additional recommendation for the temporary procedure. In order to facilitate operation, if later a radical step (cutting) seems desirable, Dr. John B. Flick ties a thread around the nerve before closing the incision. The nerve may then be identified with greatest ease.

Comment.—A diagnosis of basal pulmonary tuberculosis was made in a group of 4 patients. The manifestations on entry to the hospital were not unlike those in nonspecific pulmonary basal infections. In 2 cases the early discovery of bacilli in the sputum settled the diagnosis; in the third case repeated examinations of the sputum were necessary before bacilli were seen; in the fourth, bacilli were grown from secretions obtained by bronchoscopy from the cavity in the lung. The cases emphasize the importance of critical study of basal infections even when a diagnosis of nontuberculosis is suggested. The striking effects of collapse treatment are noted.

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mechanisms. It appears that combined artificial pneumothorax and the cutting or crushing of the phrenic nerve are unusually effective in the treatment of basal pulmonary tuberculosis. Although improvement followed artificial pneumothorax, expectoration continued until after the phrenic nerve operation had been performed. This suggests that the combined methods

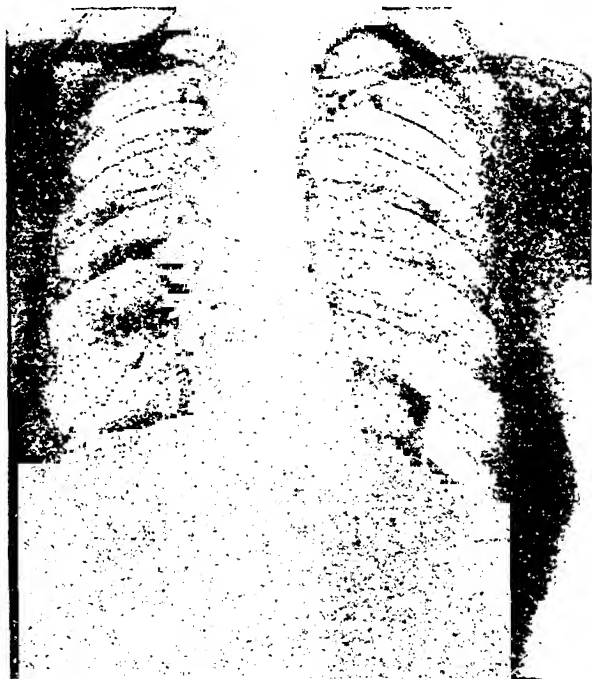


Fig. 126.—A roentgenogram showing the lung partially collapsed and the cavity shifted downward and toward the mediastinum. The cavity has undergone partial collapse. Fluoroscopic studies following phrenic evulsion showed that the diaphragm was elevated 3 cm. and the cavity compressed to about one half of the previous diameter.

are necessary to induce satisfactory collapse. The effect may be attributed to pressure on the lung from air in the pleural cavity above and pressure from the elevated diaphragm below. It may be noted that a "temporary" phrenic operation (crushing of the nerve) was selected in preference to phrenectomy (cutting of the nerve) in order to "test" the mechanism. This

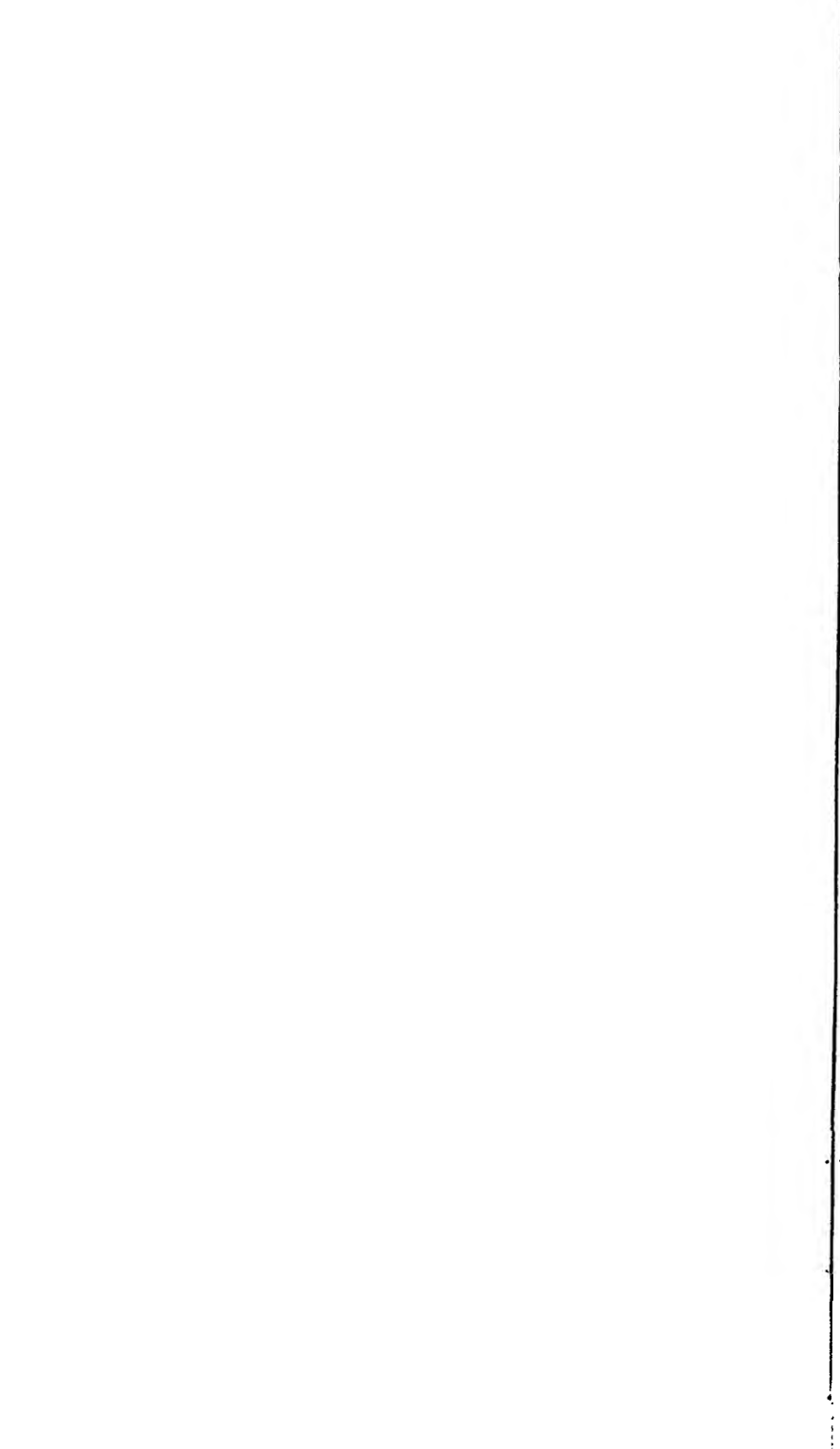
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G. SCHNABEL

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because of increasing leg weakness, he was unable to report for treatment and accordingly was readmitted to the house on March 3, 1933; during February there had been some edema of the legs, more marked on the left. The cervical swelling has always been painless. He has no other pains or aches and has good control of his urinary and anal sphincters.

He denies all previous disease until the present illness; there is no history of venereal infection.

The patient is unmarried, a shirt-cutter by occupation. Formerly he was able to walk to his work, a distance of 3 miles; from the time of onset of his present illness, he had to commute by trolley-car, and in this way was able to continue work until December, 1932, when he had to stop because of weakness.

His mother is sixty-five and his father seventy; there are six siblings between forty-five and fifty years of age, all living and well. No deaths have occurred in the immediate family.

On physical examination we find a rather underdeveloped adult white male; he is quite cooperative and volunteers the information that he has Hodgkin's disease. He is unable to walk and seems to have no power in his lower extremities except for slight adduction. There are no sensory changes. The Achilles, patellar and plantar reflexes are absent. Other reflexes are normal. Temperature 99.8 to 101 F.; pulse 120; respirations 18; blood pressure 112/74. The skin is pale and warm; no jaundice is present. There are two scars above the left clavicle, sites of biopsy. *Lymph nodes* of the left supraclavicular region are visibly prominent, being quite discrete and not tender; the overlying skin is not adherent; nodes of the right cervical, both axillary and both inguinal regions are distinctly palpable, discrete, free from tenderness, but not visibly enlarged. The *head*, ears, nose and eyes appear normal; pupils react to light and in accommodation; there is no palpebral ptosis and there are no extra-ocular palsies. There is suspicion of dental infection; tonsils are not unusually large and do not appear diseased. *Chest* expansion is fairly good, sides being equal; the lungs are normally and equally resonant throughout; no râles are heard. The area of *cardiac* dulness is not enlarged; the sounds are clear.

the rhythm regular and there are no murmurs. Radial vessels are not unusually palpable. The musculature of the *abdominal* wall is flabby, there is slight distention. The spleen is not palpable; no other organs nor masses can be felt. The *extremities* are emaciated; there is no edema at the present time. A healing blister is noted on the right heel.

DR. SCHNABEL: At this stage in your examination were you inclined to accept the patient's volunteered diagnosis of Hodgkin's disease?

MR. SMITH: Yes, but only tentatively.

DR. SCHNABEL: I assume, then, that you had some other differential diagnoses in mind. If so, what were they?

MR. SMITH: Tuberculous lymphadenitis, leukemic lymphadenosis, luetic lymphadenopathy, a neoplasm involving the lymph nodes (perhaps sarcoma or metastatic carcinoma), and possibly a reticulo-endotheliosis.

DR. SCHNABEL: Did you exclude your first tentative diagnosis of tuberculous lymphadenitis?

MR. SMITH: Yes, but this is rather difficult to do, unless one examines biopsied lymph node material. It is, however, unlikely that they are tuberculous nodes because the general physical examination, physical and x-ray examination of the chest and spine, did not point to another acid-fast lesion. The nodes themselves showed no calcification shadows by x-ray study. They are discrete, not tender and the skin is not adherent.

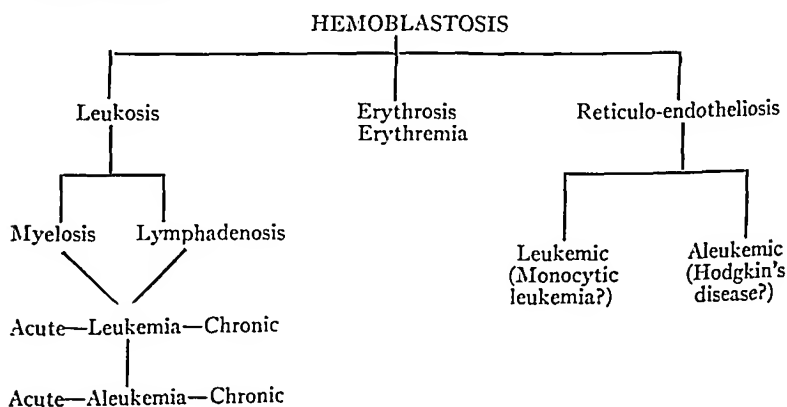
DR. SCHNABEL: What evidence have you to exclude a leukosis as a diagnosis?

MR. SMITH: The blood counts are evidence against the leukemic leukoses. They were on December 23, 1932 (previous admission): Erythrocytes, 4,230,000; leukocytes, 11,200; hemoglobin, 90 per cent; neutrophils, 72 per cent; lymphocytes, 24 per cent; monocytes, 4 per cent; on March 6, 1933: Erythrocytes, 3,100,000; leukocytes, 9600; hemoglobin, 60 per cent; neutrophils, 83 per cent; lymphocytes, 15 per cent; monocytes, 2 per cent.

DR. SCHNABEL: Do these counts rule out an aleukemic leukosis? How does one establish such a diagnosis?

MR. SMITH: Such a hemogram only rules out a leukemic form. Microscopical sections of the nodes should tell us whether we are dealing with an aleukemic leukosis.

DR. SCHNABEL: Mr. Smith and I have been using terms which are comparatively new in medical parlance. I hope it is well understood that objection has recently been made to the term "leukemias" on the ground that these are not really diseases of the blood, as the word *per se* suggests, but rather of the blood-forming organs. This being so, it has been thought better by some to use the term "lymphadenosis" for the older "lymphatic leukemia" and "myelosis" for the older "myelogenous leukemia," and "leukosis" a general term for either form. If the circulating blood presents qualitative or quantitative evidence of the disease in the parent tissue, then the term "leukemic" is prefixed, and if it is absent, then "aleukemic" is applied. The same terminology is applicable to diseases of the reticulo-endothelial system. Orth suggested "hemoblastosis" to include all diseases of the hematopoietic tissues in which there occurs a "great cellular overgrowth together with alteration in the structure of the newly formed cells." Piney tabulates the situation in this fashion:



To those of us accustomed to the older terminology, this seems very rational. Are these nodes the seat of a luetic lesion?

MR. SMITH: Not very likely, in the absence of a positive Wassermann. After I had made my notes I learned from Dr.

Leivy that the "shots" referred to in my records were cacodylate of soda, directed toward Hodgkin's disease for its arsenic effect.

DR. SCHNABEL: How can one confirm or disprove the other tentative diagnosis you made here?

MR. SMITH: By knowing what the sections of these nodes show under the microscope, stained in the usual ways and by special methods.

DR. SCHNABEL: Biopsy certainly would seem to be at the present time the court of last resort in the field of lymph node disease diagnosis. On the other hand, it is by no means an absolutely final method. Some nodes would seem to defy diagnostic opinion, and others call forth conflicting opinions from different pathologists.

Dr. Custer, will you kindly tell our group what you found in both the first and second excised nodes?

DR. CUSTER: As Mr. Smith has told you, the first biopsy was reported "questionable Hodgkin's disease" at another hospital. I had rather the advantage of the pathologist there, in that there was available for my study not only his slide, but preparations of my own taken at a considerably later date; in the interval, the disease process had advanced and cleared the picture somewhat.

I did not see the first node that was removed and cannot give you a gross description. The section shows the normal architecture to be lost, except for the persistence of occasional lymph follicles; the sinuses are hardly identifiable. This distortion is due to a uniform hyperplasia of comparatively large cells with vesicular nuclei, varying in shape from spindle to polyhedral and stellate forms, an occasional one being phagocytic; here and there a multinucleated form is seen, not presenting the appearance, however, of characteristic Reed-Sternberg cells. Transition forms between the predominant cell type and histiocytic cells of the general reticulum and sinusoidal endothelium suggest their reticulo-endothelial origin.

The second node removed was quite large, measuring 4 x 2 x 1 cm.; it was firm in consistency and the cut surface a homogeneous pearly gray-white color. Section shows the hy-

perplastic process in a considerably more advanced state, the architecture being practically completely effaced. The same cell type is present, but in somewhat more anaplastic form and disorderly arrangement. There is no concomitant hyperplasia of the lymphoid elements of the node; rather are both diffuse lymphoid tissue of the pulp and lymph follicles destroyed through

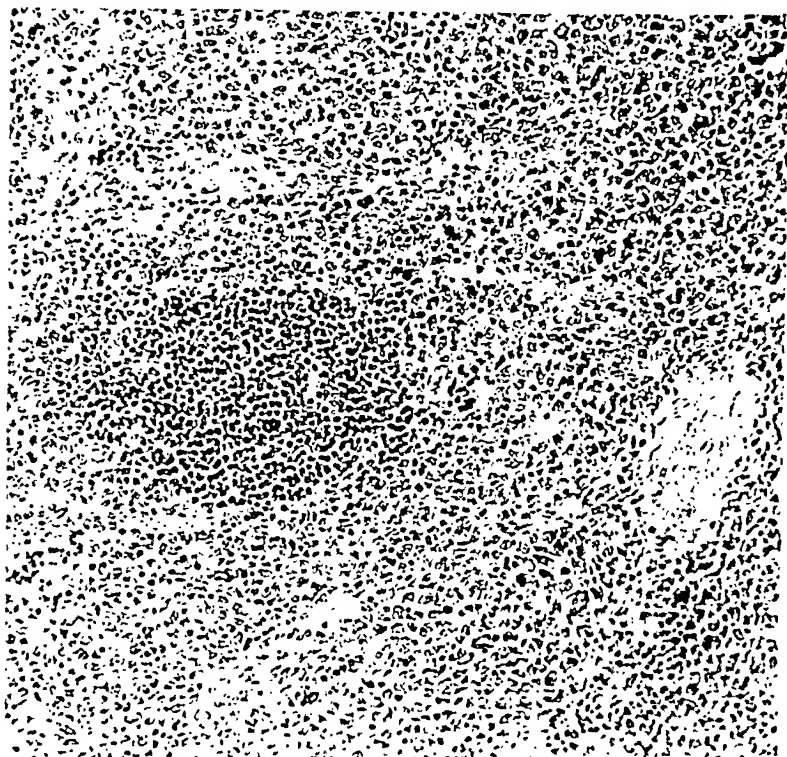


Fig. 127.—First biopsy. Architecture is destroyed through proliferation of reticulo-endothelial elements. The remnant of a lymph follicle is seen in the center. A few giant cells are visible. ($\times 175$.)

a proliferation that is confined exclusively to cells of the reticulo-endothelial system.

I think that a rather minute description of the cells is important. They present a varied morphology, some being round, resembling the monocyte, others polyhedral; the majority are spindled or stellate, with long, delicate, cytoplasmic proc-

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The second node removed was quite large, measuring $4 \times 2 \times 1$ cm.; it was firm in consistency and the cut surface a homogeneous pearly gray-white color. Section shows the hy-

emphasized by Maximow's azure II-eosin stain. The nuclei are round, oval, or indented, being vesicular and of spongy structure, with exceedingly delicate chromatin strands, among which are interspersed fine granules; a number contain from one to three prominent nucleoli. The perinuclear mem-

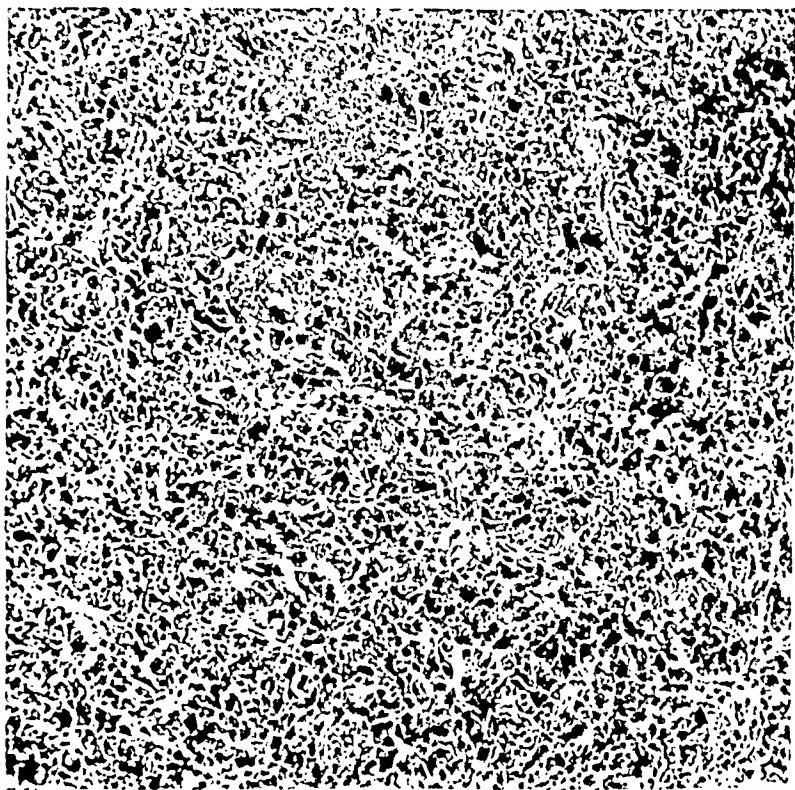


Fig. 129.—Second biopsy. Architecture is completely obliterated. Cells have assumed a more anaplastic and irregular form than those of the first node examined. More giant forms appear here. ($\times 175$.)

brane is narrow, but sharply defined. Giant cells are seen frequently and present a variety of appearances; some are simply a large, multinucleated syncytium; others contain a huge, single nucleus that is cleft and distorted; an occasional form is seen that fits Dameshek's description of "unilocular giant cells, *i.e.*, they contain a large, twisted, irregular, basket-shaped nucleus

esses, some of which can be traced far into the surrounding area; these processes furnish a sort of stroma that is quite independent of the normal stroma of the lymph node, although remnants of the latter persist and support the vascular channels (this is demonstrated best by Mallory's aniline blue stain). In the

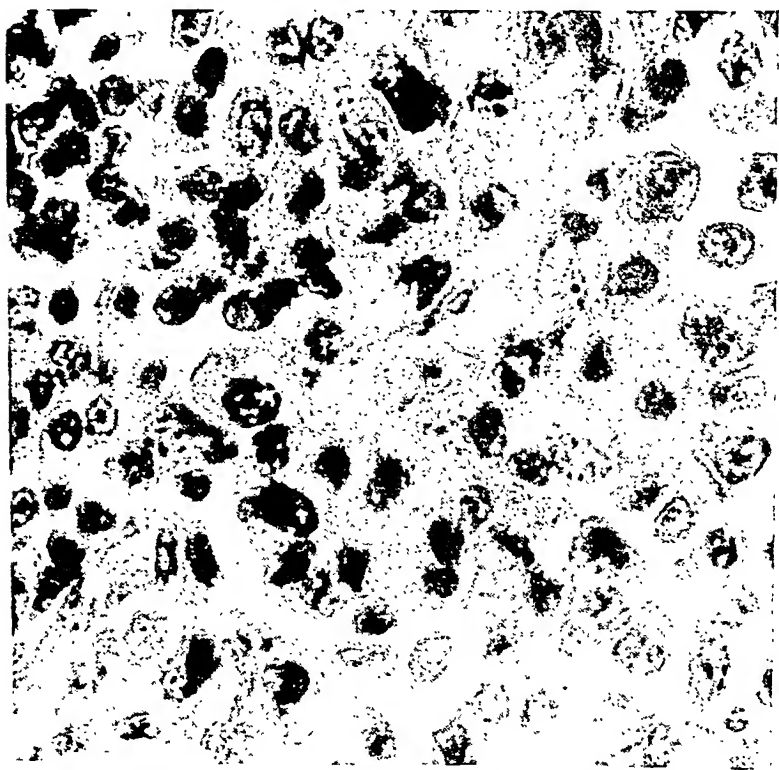


Fig. 128.—First biopsy. Shows margin of lymph follicle seen in Fig. 127, with lymphocytes in upper left and proliferating reticulo-endothelial elements occupying remainder of field. Some of latter are round, free and present morphology of the monocyte. ($\times 1000$.)

routine hematoxylin-eosin preparations, the cytoplasm is distinctly basophilic, often with a faint pinkish glow in the region of the nucleus; many of the cells are vacuolated and some contain phagocytosed material (erythrocyte fragments and non-descript tissue debris); the basophilia and vacuolization are

aleukemic reticulosis and rethelsarcomatosis. (Incidentally, I believe the question mark placed by Piney after "monocytic leukemia" is quite superfluous; this is a well-established disease entity.) The first two show essentially the same histopathologic picture of generalized histiocytic proliferation, especially marked in lymph nodes, spleen, bone marrow and liver, differing in that the first is characterized by a leukemic blood picture, the

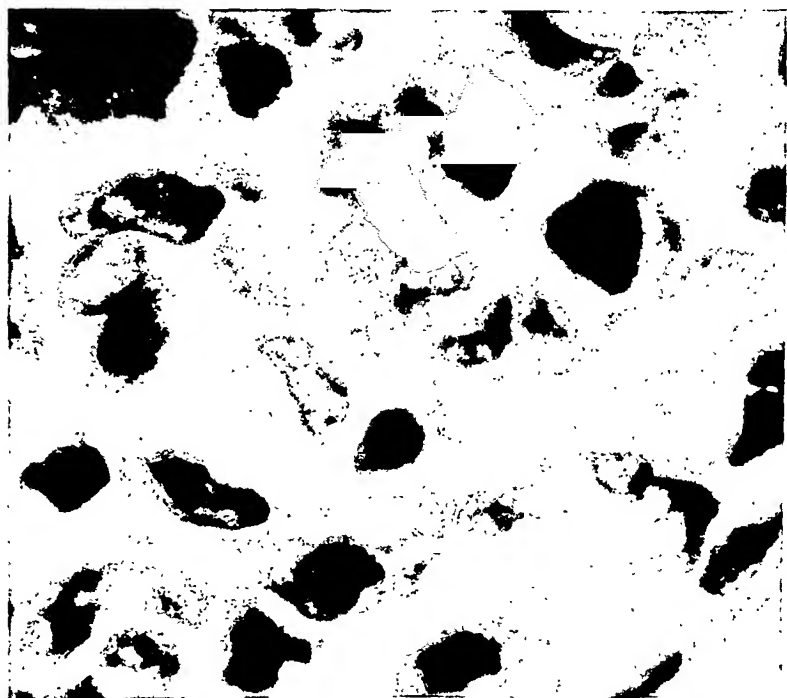


Fig. 131.—Second biopsy (through less dense area). The cytoplasmic processes stand out clearly and vacuolization is prominent. A phagocytosed erythrocyte is seen in the upper right. ($\times 1450$.)

cells being monocytes or their progenitors; each shows what Dameshek calls a "destructive" type of anemia (*i. e.*, anemia, leukopenia and thrombocytopenia) that is progressive, due to replacement of the hemopoietic tissue of the marrow. The last type usually begins in a single locus and infiltrates and metastasizes in a true sarcomatous fashion; the neoplastic cells are of the same type.

ramifying throughout the cell." Some of the giant forms resemble the Reed-Sternberg cell of Hodgkin's disease. No eosinophils are seen and tendency to sclerosis is not very prominent.

We believe then that these cells are histiocytes and that our case is one of the proliferative diseases of the reticulo-endothelial

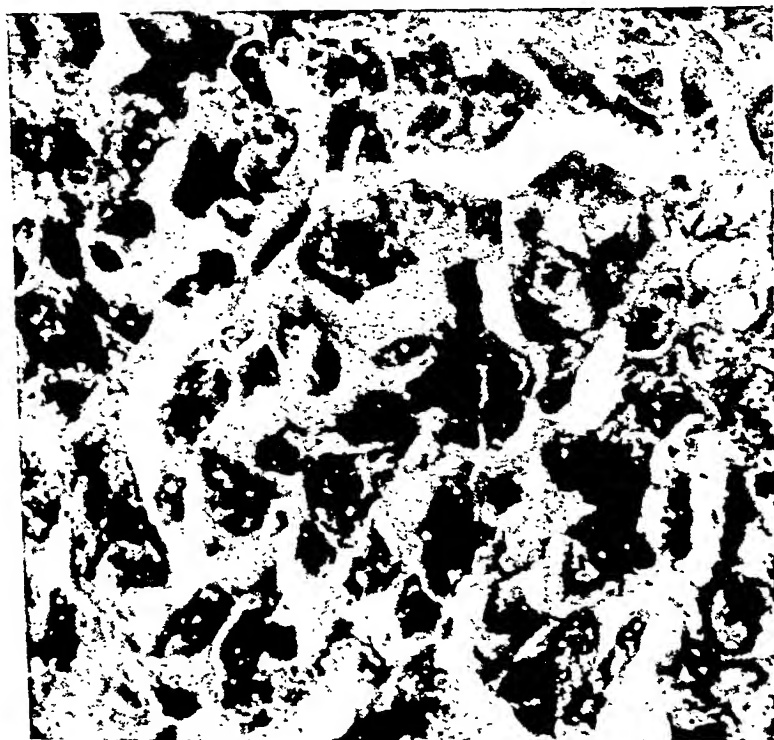


Fig. 130.—second biopsy (through dense area). The spindled to polyhedral cell forms are predominant; characteristic vesicular nuclei are well shown. A giant cell lies just above the center. ($\times 1000$.)

system, *i.e.*, a reticulo-endotheliosis (reticulosis). In the absence of changes in the circulating blood, other than a mild anemia, we can classify it further as an aleukemic reticulosis.

DR. SCHNABEL: What do you classify under proliferative diseases of the reticulo-endothelial system?

DR. CUSTER: Leukemic reticulosis (monocytic leukemia),

further and considered Hodgkin's disease a "megakaryoblastoma"; I am not in sympathy with this interpretation.

MR. SMITH: Dr. Schnabel, do you think I should have made the diagnosis of aleukemic reticulo-endotheliosis clinically?

DR. SCHNABEL: I think you did exceptionally well to narrow the diagnosis down to Hodgkin's disease, the aleukemic leukoses, aleukemic reticulosis and malignant lesion of the lymph nodes. The diagnosis of Hodgkin's disease and aleukemic reticulosis depend on their histopathologic picture. Clinically it is quite impossible to be certain; this is true of many of the lymph node diseases. In the present instance the patient is seen with the lymph node enlargement most prominent in the neck, without splenomegaly and without striking anemia, with slight leukocytosis and no significant alteration in the blood picture; certainly one would be more inclined to think of Hodgkin's disease than of an aleukemic leukemia or reticulosis.

Given a patient, however, with generalized lymphadenopathy, splenomegaly of moderate degree, "destructive anemia" that is progressive, and recurring fever (as some of the reported cases have shown), the converse might be true. Hodgkin's disease is characterized by lymph node enlargement that is at first confined to one or several chains and an anemia that appears usually rather late. Of the leukoses, the myeloid type is practically always accompanied by massive splenomegaly; by exclusion we would think of lymphadenosis or reticulosis. The final diagnosis rests with the lymph node or sternal marrow biopsy.

Whether we regard such lesions presented by this man as Hodgkin's disease, or, as the newer order would have us do, as aleukemic reticulosis, the prognosis would seem to be the same. Both are fatal after a variable period of time. I have the impression that the reticulositic variety is rather shorter lived, although Hodgkin's disease may run an acute short course. What has been looked upon in the past as acute Hodgkin's disease may have been unrecognized reticulosis, however. Both these lesions are radiosensitive. Apparently our patient's nodes are particularly so.

DR. SCHNABEL: In what respect does the histologic picture that you have described in this case differ from that of Hodgkin's disease?

DR. CUSTER: Hodgkin's tissue usually impresses me as being of more granulomatoid nature. The same obliteration of nodal architecture occurs; the same proliferation of reticulo-endothelial elements exists, as well, but not in the pure form that we see in our case. Rather is there in the so-called "cellular stage" a somewhat heterogeneous admixture of these cells with lymphocytes (and, in the majority of cases, eosinophils); the typical Reed-Sternberg cells are usually smaller than those that I have described, with one or several distinct nuclei, often overlying one another; larger forms are occasionally seen, however, that contain "biscuit" nuclei. The tendency to sclerosis seems greater in Hodgkin's disease.

Dameshek points out, however, and justly so, certain similarities, both clinical and pathological, between these two diseases and suggests "that aleukemic reticulosis may be a generalized form of Hodgkin's disease, and, conversely, that the latter disease as ordinarily found, may be a more localized form of reticulum cell proliferation." It is possible that my differentiation may be more apparent than real.

DR. SCHNABEL: Do you believe the Reed-Sternberg cell to be a specific cytological entity associated with Hodgkin's disease alone?

DR. CUSTER: Emphatically not! Genetically I believe them identical to the giant cells in our present case; morphologically they seem a little different. They are both derivatives of reticulo-endothelial system. Occasionally one sees cells identical to the Reed-Sternberg cell in a simple hyperplastic splenic pulp.

Not long ago Medlar believed that he could identify the Reed-Sternberg cell as a megakaryocyte. This is not as strange as it may seem; in experimental animals I was able to demonstrate the derivation of megakaryocytes from cells of the reticulo-endothelial system as part of a diffuse myeloid metaplasia in spleen, liver and lymph nodes.¹ It would seem then that the same stem cells exist for all these giant forms. Medlar went

It would be interesting to discuss other features which this patient presents, for example his neurological symptoms, which seem to perplex our neurological consultants, Drs. Wilson and Ornsteen. His spinal fluid shows a paretic curve with no serological evidence of syphilis. Hodgkin's disease on occasions presents certain central nervous compression signs and symptoms, but they are usually quite different than those of this patient's. Then, too, we might speculate as to whether our patient's slowly developing anemia is the result of radiation or of a replacement of hemopoietic tissue in his bone marrow by proliferating histiocytes, whether his oral infection has played an etiological rôle, and why he has had some lower extremity edema. He does not seem to have a pelvic tumor. I think it will be enough to have called attention to this proliferative disease of the reticulo-endothelial system; one which is really but a few years old from the standpoint of recognition, but one of which all of you must become medically conscious.

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of the disease, the tendency to remissions, are similar to those of true Graves' disease; also when the symptoms subside in severity, they all disappear simultaneously, as is the case in Graves' syndrome. The exophthalmos in the *forme fruste* becomes manifest sooner or later during the course of the disease.

In "thyroidismus" or hyperthyroidism symptoms are predominantly referable to the nervous or the circulatory systems; here there is no exophthalmos or an enlargement of the thyroid gland, and the clinical course is distinct entirely from the "formes frustes" as well as from true Graves' disease. The condition runs a more chronic course; it may commence with a single symptom, which symptom increases in severity in paroxysms. Thus one may find a patient with a rapid fibrillating heart, or cardiac decompensation, or angina pectoris, and all other usual symptoms of hyperthyroidism may be lacking. Another patient may be apathetic or present labile psychic states; depressive and manic. The severity of the symptoms is independent of each other. These cases are hard to prove to be sufferers of thyrotoxicosis, and many of them are treated for something else until the true condition is discovered. It is noteworthy that very rarely does a case of thyroidismus ever develop true Graves' disease.

The 2 cases presented below illustrate some of the points under discussion:

Case I.—Miss F. P. aged thirty-four, cook, was in apparent good health until May, 1932; she suffered then from an upper respiratory infection which cleared up after four weeks; soon afterward her feet began to swell as the day advanced; this would clear up after a night's rest. By the end of June the swelling extended up to the thighs. In addition she had some shortness of breath, especially upon climbing stairs. On August 2nd, the patient was caught in a rain-storm and her condition grew worse. She was admitted to the Philadelphia General Hospital (service Dr. Wm. Egbert Robertson) on August 5, 1932, with complaints of shortness of breath, swelling of the ankles and legs and nocturia. Her best weight was 142 pounds seven months ago; her present weight is 130 pounds. The main points in the physical examination of the patient were: Eyes, slight exophthalmos; the pupils responded to light and accommodation. Thyroid not palpable; lungs, moist crepitant râles over both bases and right hydrothorax; heart, apex sixth interspace, 13 cm. from midsternal line; palpable systolic thrill over precordium. Right border 5 cm. from midsternal line. The rate at the apex was very rapid and somewhat irregular; marked blowing systolic murmur with

CLINIC OF DR. MICHAEL G. WOHL

TEMPLE UNIVERSITY AND PHILADELPHIA GENERAL HOSPITAL

HYPERTHYROIDISM MASKED AS (a) MALIGNANT HYPERTENSION, (b) AURICULAR FLUTTER, AS ILLUSTRATED BY TWO CASES

THE clear-cut clinical syndrome of Graves' disease offers few difficulties in diagnosis. The exophthalmos, the tachycardia, the tremors, the loss of weight, the moist skin and the muscle weakness, especially of the quadriceps femoris, and the elevated basal rate, make certain the diagnosis. Not all of these symptoms are constantly present; neither are they all to be attributed to a thyroid dysfunction. Thus a person belonging to the autonomic imbalance group may manifest a good many symptoms observed in patients with exophthalmic goiter, which in reality are due to sympathetic stimulation such as sweating, tachycardia, tremors, flushing, "luster" of the eyes and even the Möbius sign. The presence of a goiter in such a person makes it quite difficult to distinguish this group of patients from those suffering with true hyperthyroidism.

Hyperthyroidism, or what Chvostek, Jr.,¹ designates as "thyroidismus," is to be differentiated from Graves' disease and its atypical types the "formes frustes basedowi." The former present a well-defined type of human individual, the "Graves' constitution" described in this country by Warthin² or the "thymic lymphatic constitution," which according to Chvostek is the general pathologic picture of Graves' disease.

The formes frustes are really cases of Basedow disease, during the course of which one of the cardinal symptoms may be missing, such as exophthalmos, tachycardia, or enlargement of the thyroid gland. Indeed, in some instances, instead of tachycardia there may be actually a bradycardia; however, the onset

14th was plus 21. Because the basal metabolic rate failed to come down to normal, and because of the unsatisfactory response of the heart to therapy, the existence of hyperthyroidism was suspected. Patient was placed on compound solution of iodine, 10 minims t.i.d. She improved markedly, the pulse rate slowed down and the basal rate reduced to minus 4 per cent. It was decided that this was the most opportune time for operation. A subtotal lobectomy was done by Dr. Righter. The patient made an uneventful recovery and left the hospital



Fig. 133.—High-power photomicrograph of thyroid tissue from Case I. Note the marked focal infiltration of lymphocytes.

ten days after the operation. The histologic examination of the tissue by Dr. R. P. Custer showed it to be a hyperplastic toxic goiter with lymphoid hyperplasia.*

Four months later the patient was reexamined. Her general condition was markedly improved. The basal rate was plus 7 per cent; pulse 92; blood pressure 200/120. She gained weight.

*The lymphoid hyperplasia is regarded by Chvostek as evidence of a thy-micolymphatic constitution in Graves' disease.

accentuation of first sound. Very faint diastolic rumble. Pulmonic second was greater than aortic second. Systolic murmur at aortic area with diminished second sound. Pulse rate 140, blood pressure 160/120. Abdomen; liver edge palpable three fingerbreadths below the right costal margin; spleen was palpably enlarged. There was dullness in both flanks. Anteriorly over the abdomen there was tympany. Lower extremities revealed slight pitting of ankles. Reflexes were normal. The provisional diagnosis was hypertension, auricular fibrillation with cardiac decompensation; hyperthyroidism (?). Because of patient's grave circulatory embarrassment, 8 ounces of blood was removed by venesection; also 400 cc. of fluid was removed from the right chest.



Fig. 132.—Forme fruste basedowi.

Within two hours she improved. Further studies showed the following: Basal metabolic rate was 39 per cent above normal. The urine contained a trace of albumin, specific gravity 1.015; otherwise no abnormalities were noted. The blood count showed a secondary anemia. Blood Wassermann was negative, blood urea 10 mg. per 100 cc. of blood. Electrocardiogram showed rapid fibrillation. Strophanthin, 1/66 grain, was given intravenously. The pulse was much slower and more regular (rate 110). A basal rate August 17th (twelve days after admission to the hospital) was plus 15; on August 18th, plus 13 per cent.

An electrocardiogram showed auricular fibrillation, but the pulse rate was much slower and more regular. She was given a course of digitalis; she continued to improve and was permitted to sit up in bed.

On October 10th on limited exercise the pulse became rapid, 120 beats per minute, and more irregular. A basal metabolic rate determination on October

the midclavicular line. There was also dulness in third interspace to the left. A systolic murmur was heard at the apex; the liver was not tender, but the edge of the liver was palpable 1 cm. below the right costal margin. The Wassermann reaction was negative. The blood count showed a secondary anemia and the urine contained a trace of albumin, but the total twenty-four-hour output was rather scanty. An electrocardiogram showed an auricular flutter with a 2 to 1 block, the ventricular rate being 150 per minute.

The patient was placed on 30 minims of tincture digitalis every four hours and after four days the flutter was converted in fibrillation with a ventricular rate of

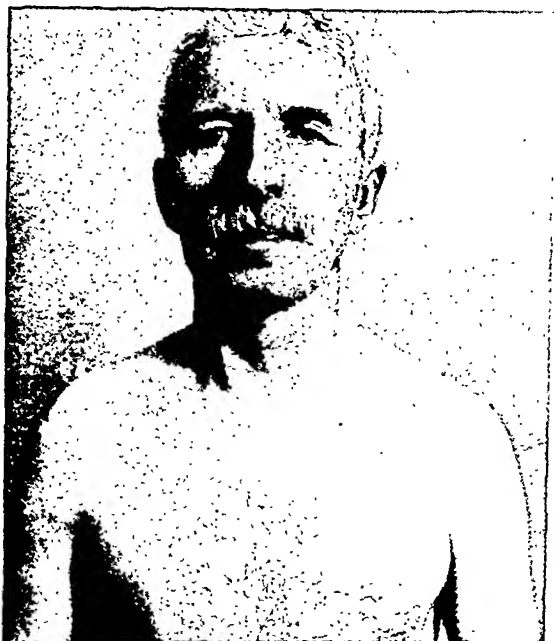


Fig. 134.—Hyperthyroidism. Note apathetic appearance of patient.

110. In view of the fact that the patient refused to be hospitalized, I thought it risky to prescribe quinine.

The digitalis was withdrawn, but in seven days the flutter had returned. The patient was complaining of feeling warm and his nervousness has increased. A basal metabolic rate determination on February 24th showed a reading of plus 41 per cent. He was placed on 15 minims (1 cc.) of compound solution of iodine three times a day and tincture of digitalis, 15 minims, three times a day. Ten days later the basal metabolic rate was reduced to plus 21; he was still fibrillating, with a heart rate of 90. He regained his strength, the urine increased in quantity and the heart appeared to be in a fair state of compensation. Thyroidectomy was advised, but the patient refused to be operated on. He received a series of x-ray treatments by Dr. W. Edward Chamberlain. The basal rate at

Comments.—This patient presented a clinical picture of cardiac decompensation and auricular fibrillation, as is often observed in patients with hypertension. Even after prolonged observation in the hospital, it was difficult to decide whether the patient was suffering from hypertensive vascular disease or hyperthyroidism complicating the hypertensive state. The elevated basal metabolic rate was not much helpful in the differential diagnosis, since in cardiac decompensation and in hypertension the basal rates are frequently above the normal. In our experience the basal rate in essential hypertension averages plus 27.7 per cent. The loss of weight and the easy fatigability likewise occur in hypertension. The fact that the administration of iodine was followed by marked improvement and a fall in the basal metabolic rate to minus 4 spoke for the coexistence of a thyrotoxicosis. The histologic examination of the thyroid tissue and the course of the disease would indicate that the condition is of the “*formes frustes basedowi*” type. Another significant point brought out by this case is that thyroidectomy did not apparently lower the arterial tension. Becker³ has advocated thyroidectomy in malignant hypertension. Rose⁴ reported recently a case similar to ours where thyroidectomy had no influence on the course of malignant hypertension.

Case II.—Mr. E. M., aged fifty-six, when first seen on February 9, 1932, was complaining of palpitation, flatulence, extreme weakness and periodic attacks of shortness of breath. In the past twelve months he lost 20 pounds in weight and became nervous and excitable.

The present illness dates back to one year ago, when because of the dismissal of a co-worker his work and responsibilities materially increased. He noticed then that he tired more readily and became restless. He was losing weight progressively. During this time he complained of attacks of palpitation of the heart, lasting twenty minutes to one hour. These attacks became more frequent and ten days prior to his visit to the office, he commenced to experience shortness of breath. Patient previously has enjoyed good health, never smoked and never used alcohol.

Examination revealed a large man, weighing 169 pounds, with a normal temperature, blood pressure 120/85, pulse 120. The patient presented an apathetic appearance. The skin was moist; the head, eyes and neck were normal. There was no exophthalmos and no goiter. The chest was emphysematous with fine moist râles at both bases posteriorly. The heart was grossly irregular in rate and rhythm, tumultuous and the cardiac dulness extended 1.5 cm. to the left of

Neither x-ray nor surgical therapy for thyrotoxicosis will be further entertained by the patient.

Comments.—The auricular flutter in this patient is logically to be attributed to the hyperthyroidism, since no other etiologic factor could be elicited as the cause of his cardiac state. Furthermore, with a coincident general improvement in the hyperthyroidism resulting from the x-ray and iodine therapy, his cardiac condition has consistently improved. It is regrettable that in view of the circumstances, we could not resort to quinidine therapy, which might have converted the fibrillation into a normal rhythm. However, the patient was brought to a state where he could be about with considerable comfort.

Cardiac disturbances in hyperthyroidism are of frequent occurrence. The sinus tachycardia, premature extrasystoles and murmurs may not necessarily indicate serious cardiac damage. Fibrillation and flutter are, however, of greater clinical significance. Next to mitral stenosis, thyroid intoxication is the second common cause for fibrillation.

Fibrillation occurred in one fourth of the cases of thyroid intoxication reported by Willius⁵ and his associates. Cardiac decompensation and auricular fibrillation that fail to respond to the usual treatment should arouse the suspicion of an underlying hyperthyroidism. Flutter is of less common occurrence in hyperthyroidism. Krumbhaar⁶ has found only one case of auricular flutter in his series of 51 goiter patients, and Willius⁷ and his associates have observed flutter in two patients out of 377 cases of exophthalmic goiter or adenoma with hyperthyroidism.

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7. Willius: *Loc. cit.*

this time was still plus 24 per cent. Two weeks later the basal rate came down to plus 14. To control the heart rate it required the continued use of 15 minims of tincture of digitalis three times daily. With this dose the patient was able to be about, but omitting the dose resulted in distress.

He returned for observation on October 14, 1932. He gained 2 pounds in weight since his last x-ray treatment (in June, 1932) and he claimed to feel sub-



Fig. 135.—Seven-foot ventral projection of thorax of Case II, demonstrating marked enlargement of left auricle as well as of the ventricular portions of the heart. (Courtesy of Dr. W. E. Chamberlain.)

jectively better. His blood pressure was 115/80. Fibrillation was still present. Heart rate 115 with a moderate pulse deficit. Basal metabolic rate plus 20. Four months later he returned having lost 10 pounds since October, 1932. He was complaining again of being weak and had attacks of shortness of breath. The basal rate was plus 26. Heart showed auricular flutter, some evidence of early decompensation. Blood pressure 110/80. He was placed on the conventional treatment for cardiac decompensation and on compound solution of iodine.

CLASSIFICATION OF THE INFLAMMATORY ARTERIAL DISEASES

- | | | | |
|--------------|---|---|----------------------------------|
| (A) Acute | { | 1. Primary: Arteritis and thrombo-arteritis. | |
| | | 2. Secondary: Complications in acute infections. | |
| (B) Subacute | { | 1. Endarteritis obliterans | { |
| | | | (a) Infectious. |
| | | | (b) Luetic, tuberculous. |
| | | | (c) Physiologic. |
| | | | (d) Indeterminate or indefinite. |
| | | 2. Polyarteritis or periarteritis nodosa. | |
| | | 3. Mycotic and embolic aneurysms. | |
| (C) Chronic | { | 1. Thrombo-angiitis obliterans (Buerger's disease). | |
| | | 2. Arteriosclerosis. | |
| | | 3. Atheromatosis (diabetic). | |

The above classification is suggested for grouping the various forms of arteritis. It is purely an arbitrary one and should not be considered inflexible. No doubt some of the cases of polyarteritis nodosa and endarteritis obliterans and even Buerger's disease may have an abrupt onset which may be as intense as acute arteritis. However, the first group has been reserved for those cases which present evidences of arterial disease with hemorrhages and gangrene, hitherto unrecognized and usually not diagnosed as an arteritis. This applies to the so-called "primary form." That form of arteritis with gangrene complicating a well-known acute infectious disease needs no comment here. The subacute and chronic groups embrace arterial diseases which have already been accepted.

(A) **Acute Arteritis.**—It is not rare to find arteritis appearing as a complication in acute infections. Case reports have appeared in the literature of gangrene resulting from vascular damage in such diseases as typhoid fever, pneumonia, meningitis, influenza, malaria, diphtheria, rheumatic fever, septicemias and others. In these instances it is assumed, but not necessarily proved bacteriologically, that the pathologic process is attributed to the organism of that particular infection.

However, there are other conditions that have been described, appearing as idiopathic, symmetrical or spontaneous gangrene, where the underlying pathology is undoubtedly arterial but unaccounted for by the presence of a definitely

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INFLAMMATORY DISEASES OF THE ARTERIES WITH PARTICULAR REFERENCE TO THE MORE ACUTE FORMS

DISTURBANCES of the vascular system, although more or less frequently discussed in medical literature in recent years, represent a comparatively new field in medicine. It would be impossible to take up this subject from all angles. We shall, therefore, limit ourselves to some of the more acute phases of arterial diseases and briefly describe the others.

The tendency has been to group the vascular diseases into the occlusive and spastic forms. The former group embraces those conditions which result in encroachment upon the lumen of the vessels, either by proliferation of cells from the intima, thrombotic formation, or embolic phenomena. The latter (spastic) group includes those conditions in which spasm of the arteries and arterioles takes place, such as Raynaud's disease, the most classical form of vasospastic disorders; and the different forms of angiospasm due to indefinite or indeterminate origin. Another form may be mentioned when discussing arterial disturbances, the vasodilatation group, best exemplified by erythromelalgia.

Interest in the inflammatory diseases of the arteries has been stimulated chiefly since the excellent contributions of Buerger who may be looked upon as a pioneer in this field. His work on thrombo-angiitis obliterans has helped considerably in correcting the erroneous views on various forms of gangrene and vascular diseases. However, our knowledge of the processes involved in the pathogenesis of these disorders is still incomplete.

For convenience, the inflammatory diseases of the arteries are here arranged in tabular form:

cate a definite pathology of the vessels. It seems logical therefore that the diagnosis should be made along the lines of arterial disease and not carelessly classified in the group of idiopathic gangrene or purpuras. The latter may be excluded from consideration by the absence of the characteristic blood findings.

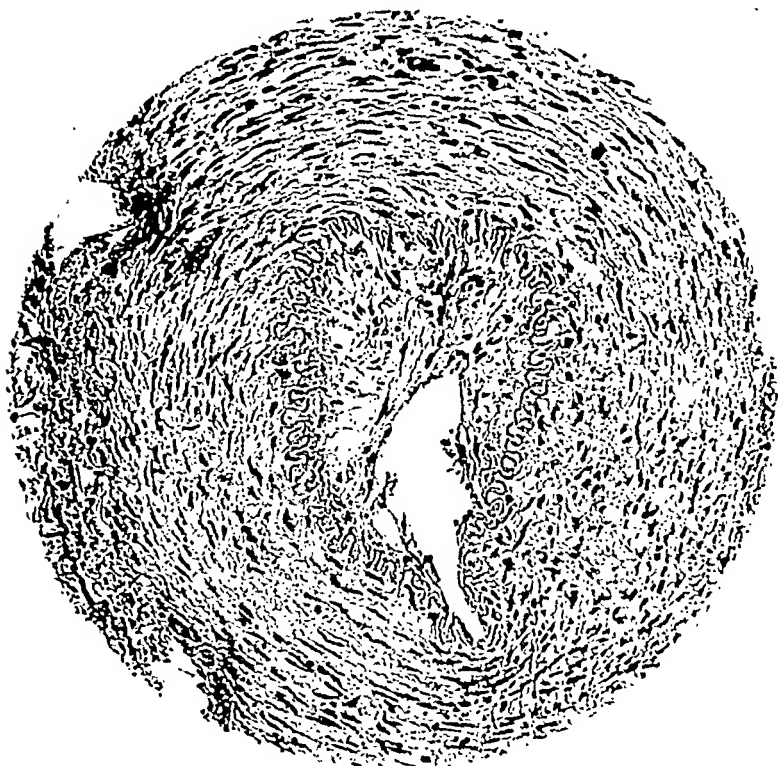


Fig. 136.—E. H. Diagnosis: Acute thrombo-arteritis. Showing marked proliferative changes of the intima and considerable narrowing of the lumen. The media is thickened and shows cellular reaction in some areas of the outer zone. This section seems to indicate an older process. Other vessels showed evidences of greater cellular activity and a more intense inflammatory reaction.

Besides purpura, the question of syphilis and thrombo-angiitis obliterans should be considered. A negative Wassermann test and the absence of any findings which might point to syphilis will rule out this disease. Buerger's may be excluded on the basis of acute onset of the disease, the negative history of

known infection. Is it not possible that we are dealing with cases of arteritis, acute in nature, produced by an infectious organism which has a predilection for vessels? This phase of arterial disease has received the scantiest consideration in the literature.

Clinical Course of Acute Arteritis.—Thrombo-arteritis may come on gradually or may make its appearance with overwhelming explosive phenomena such as pains, extensive hemorrhages, rapidly developing gangrene, and death within two or three days.

The milder forms appear with the usual picture of an acute infection, such as sore throat, headache, malaise, vomiting, and pains. Fever is present; it may be moderate, 101 to 102 F., later, it assumes the septic type, ranging from 102 to 104 F. Pain in the extremities may vary in intensity; abdominal pain is usually present. Subsequently, purpuric spots may appear, more prominently on the lower extremities. They may also be found on the body and upper extremities. Gangrene is a highly significant finding. It may appear in small areas or it may involve an entire foot. The gangrenous areas usually undergo sloughing. Amputation of the limb may be necessary to preserve life.

The *laboratory studies* revealed an increase in white cells, ranging from 18,000 to 26,000. Blood culture, bleeding, coagulation and serological studies were negative. Platelet counts were normal. *Streptococcus hemolyticus* was found in the cultures either from the throat or lesions in the extremities.

Examination of the sections shows that any sized vessel may be involved. Changes in the walls of the vessels from thickening to necrosis and varying degrees of inflammatory reaction may be seen. Thrombi are usually found, some partially and some completely occluding the lumen.

Diagnosis of acute thrombo-arteritis may be based upon the clinical picture of an acute infection with sudden onset, pains, septic temperature, leukocytosis and hemorrhagic extravasations. When these purpuric areas are associated with gangrene (especially in the presence of extensive gangrene), they indi-

cytes and plasma cells. It is presumed that the adventitia is involved first and that the cells then invade the muscular coat and, later, changes in the intima follow. Aneurysmal bulging of the diseased walls are common occurrences.

The diagnosis may be made quite readily when the superficial arteries are involved with nodular formation. The presence of such symptoms as fever, chills, pains along the vessels and nodules, all strongly suggest the presence of an infection of the arteries. Biopsy of one of the nodules will definitely help in establishing the diagnosis. Unfortunately, this is not always obtainable. The abdominal types of polyarteritis nodosa present more difficult problems for diagnosis. The involvement of the arteries need not be widespread. The diagnosis can be made only by exclusion and, quite often, this disease is recognized at autopsy.

Obliterative endarteritis at one time had the foremost rank in the group of arterial diseases. Many cases of gangrene were labeled obliterative endarteritis until Buerger proved that what was presumed to be proliferative intimal changes with occlusion was in reality a thrombus and not necessarily a piling up of cells. Whether it was coincidence or not, the fact remains that in the past twenty or twenty-five years, cases of obliterative endarteritis have been comparatively scarce.

Endarteritis may be the result of: (a) Acute infections, such as streptococcic, influenza, etc., (b) chronic infections, particularly syphilis and tuberculosis, and the more insidious forms producing arteriosclerosis, (c) physiologic, and (d) indeterminate or indefinite.

In some acute infections (a), where arteries are the targets of the pathogenic organisms, proliferative changes in the intima may be striking. This may be quite noticeable in some of the vessels, particularly of the smaller variety. However, these findings may not be uniform and under the circumstances I think such cases may be looked upon in the same light as those discussed under the heading of acute arteritis. Other cases which have appeared in the literature pertain particularly to the larger vessels, such as the aorta and pulmonary artery, where

any previous vascular disturbances, the rapid development of the gangrene and the fact that these patients may make uneventful and complete recoveries.

(B) **Subacute.**—*Periarteritis nodosa*, or as some suggest calling it, *polyarteritis nodosa*, is a rare form of arterial disease. It is believed that this condition occurs more commonly than is indicated by statistics, but unfortunately these cases are not recognized. This is excusable because in some cases the clinical picture is so obscure that the diagnosis can only be made at autopsy. Kussmaul and Maier are credited with being the first ones to describe this condition, in 1866.

The onset is not unlike that of acute arteritis with the usual early complaints, sore throat, chilliness, fever and pains. The fever may be mild and rise later, and run an irregular septic course.

Pain is a common symptom. It may be widespread over the arms and legs, along the course of the vessels. Abdominal pain is also a frequent symptom. Pains in the joints may occur.

In some cases, purpuric spots may appear on the body and the extremities. The most significant finding is the presence of nodules. They are to be found in approximately 25 per cent of the cases and vary in size. Tenderness and slight erythema are noticeable during the active stages. They may be superficial. The nodule may be attributed to either a proliferation of cells in the outer coats, especially the adventitia or it may be due to aneurysmal bulgings of the diseased and weakened walls of the artery. Nausea and vomiting are frequent complaints.

A moderate leukocytosis, with a relative increase of polymorphonuclears, is almost invariably present. Blood cultures during life or from the heart's blood at autopsies, in a certain percentage of the cases, may reveal the presence of some strain of streptococcus.

For detailed reports of the microscopic examinations of the vessel walls, the works of Ophüls and Klotz are recommended. Briefly, the characteristic findings are in the outer coats. The adventitia particularly shows marked infiltration of various types of cells—neutrophilic leukocytes, small lympho-

changes; interruption of the elastic fibers and gummatous formation. The smaller vessels usually show the most complete pictures. Occasionally cases appear with involvement of the larger arteries.

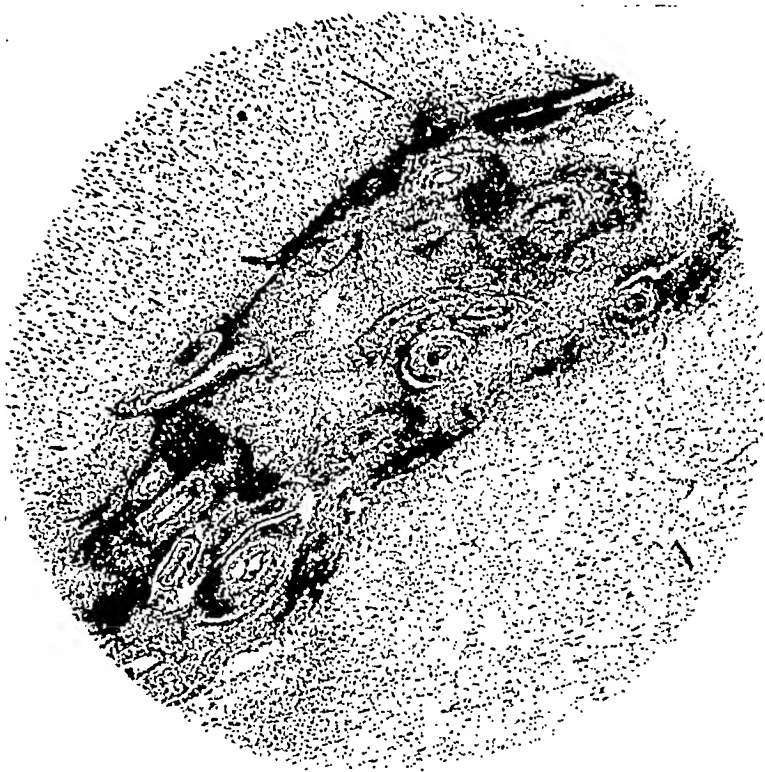


Fig. 138.—G. J. Diagnosis: Tuberculous meningo-encephalitis. Showing marked infiltration of the vessels. The infiltration involves all the coats of the arteries (panarteritis), particularly with lymphocytes and some plasma cells. Some of the vessels show degenerative changes of the intima. This is in contrast with the proliferative type of intimal reaction in syphilis.

Tuberculosis is another disease which has a tendency to produce obliterative changes in the arteries. It may appear (1) as a periarteritis, gradually extending down and involving the other coats as well, and (2) as a tuberculous endarteritis.

The *physiologic* group (c) embraces the obliterative changes

the pathologic changes may be attributed to a process extending from a vegetative endocarditis involving the leaflets.

The second group (*b*), where some chronic disease is the contributing factor, seems to be the more distinctive type of obliterative endarteritis.

Syphilis is notorious for its effect upon the vascular system.

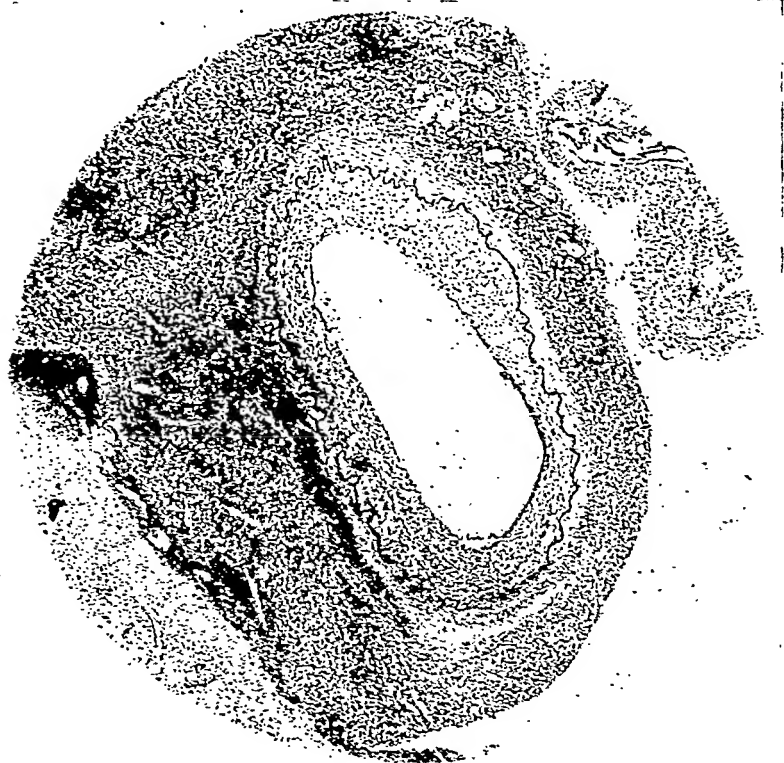


Fig. 137.—H. S. Diagnosis: Meningovascular syphilis. Showing marked proliferative changes in the intima with encroachment on the lumen. Dense infiltration (gummatous formation) in the outer walls of the vessels.

Briefly, the facts worth mentioning in reference to syphilis are: The tendency to involve the vessels of the central nervous system; the widespread distribution; proliferative changes in the intima with narrowing of the lumen; the adventitia is also often involved; the media usually presents the least pathologic

certain strains of streptococci, may produce arteriosclerotic changes in the arteries, both large and small. The findings of Benson, Smith and Semenov bear this out. Clawson, Kotz and others have produced similar changes experimenting with rheumatic fever organisms. Incidentally, it may be worth mentioning that arteriosclerotic changes have also been produced by frequent injections of adrenalin.

Diabetic Arteritis.—Clinically, it is an accepted fact that diabetics are prone to develop arteriosclerotic changes earlier in life than others. This may be explained by the presence of metabolic disturbances, the cholesterolemia and the increased susceptibility to infections.

Arteriosclerotic changes in the arteries are commonly seen in diabetes. The question is frequently raised whether or not the arteriosclerosis found in diabetics has sufficient characteristic findings to give it a separate entity. Warren evidently favors the recognition of a diabetic form of arteriosclerosis. He emphasizes the marked intimal thickening which may occur even when the other walls do not show much change. The presence of deposits of lipoid and cholesterol crystals in the intima also aids in confirming his views.

General considerations of inflammatory diseases of the arteries could take us over many fields. In this discussion, we will limit ourselves to topics of incidence and etiology. No one knows how frequently arteritis, in its varied forms, actually occurs. It is presumed to be uncommon in the average run of hospital cases. No attempt was made to learn, yet it might be of interest to know, the percentage of arterial diseases in the larger clinics. Brown collected 1118 cases of neurovascular (arterial) disturbances of the extremities, of which 795 cases were of the occlusive type (71.1 per cent). In this latter group, 372 were cases of Buerger's disease, 292 were arteriosclerosis with occlusion, and 73 were arteriosclerosis with diabetic gangrene. This collection of cases was not compared with the total number of hospital admissions. Comparative statistics might throw some light on the frequency of arterial diseases but one must bear in mind two factors that could easily cast some

occasionally the upper extremities may present the manifestations of vascular occlusion.

Arteriosclerosis has always been looked upon as a condition brought about by the wear and tear on the vessels. However, the fact that in many aged individuals the inner walls of the arteries are smooth and show no signs of pathology, and also

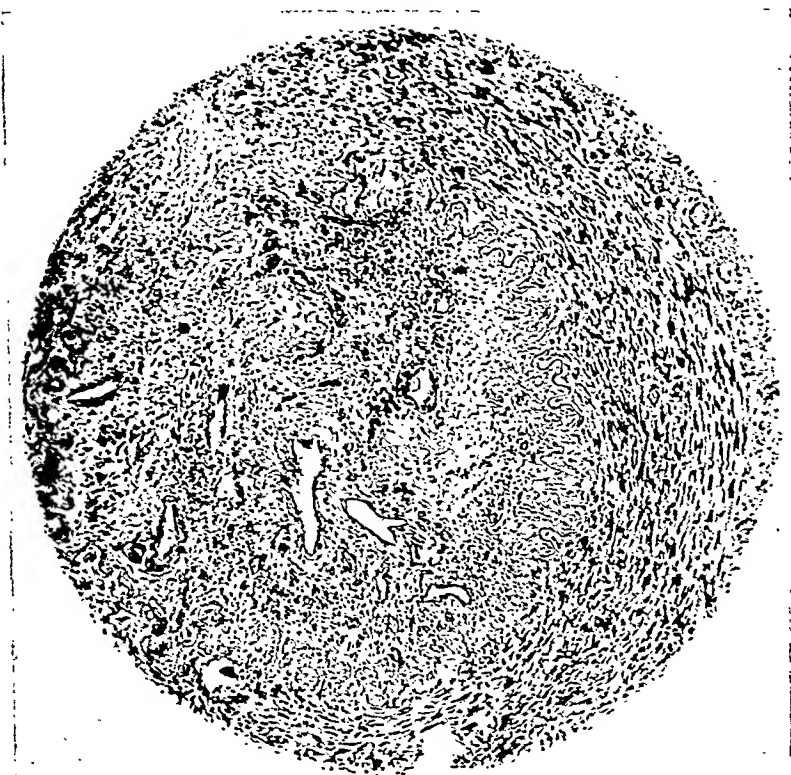


Fig. 139.—R. H. Diagnosis: Buerger's disease. Showing rupture of the elastic fibers. Total occlusion of the lumen with canalization and organization of the thrombus. ($\times 57$.)

because arteriosclerosis has not infrequently been found in young individuals who died from septicemias and rheumatic fever seem to indicate that there may be other explanations for this condition. Infection has been suspected as one of the contributory factors for some time. Experiments conclusively show that inoculations of various organisms, particularly of

ings are more consistent we may, some day, be in a position to isolate the definite micro-organisms.

In Buerger's disease, laboratory studies of the vessels and blood have been disappointing although an occasional case has been reported in which an organism was isolated. These cases are so infrequent and scattered that the results are inconclusive. The failure to find organisms, in a way, may be attributed to the fact that thrombo-angiitis obliterans may begin earlier in life and the subsequent history and signs are probably due to the after-effects and the gradually altered and deficient circulation. The opinion that we are dealing with some infection is an accepted fact. We do not know when the infection begins or how it enters. Is it not possible that we are dealing with a low-virulent infectious agent, although it may have been more active at the onset of the disease?

The *modus operandi* of arteritis can be explained only from a theoretical basis because pathologists are reluctant to commit themselves from mere examination of the sections. The intima may be involved from within the lumen or may be attacked from the outer walls inward. It is quite possible to conceive how a septic embolus lodging in a vessel may infect the intima and in other cases, particularly endarteritis of the larger vessels, by extension of the infection from a vegetative endocarditis. Endarteritis may also result from extension of inflammatory processes from the adventitia inward through the vasa vasorum. In obliterative endarteritis, it is presumed that the proliferation of the cells in the intima may be explained along the lines of response to an external irritant. The middle and outer coats are involved usually through an infectious agent entering by way of the vasa vasorum or the lymphatics. In some cases the adventitia is attacked by extension of a suppurative process by contiguity.

To summarize, one may say that the pathologic findings all point to some infectious agent, thus far unrecognized, although sporadic cases have been reported where organisms have been isolated.

The outstanding types of infectious forms of arteritis are

doubt upon percentages: First, hospitals or large clinics are apt to get selective cases and thereby raise the averages and, second, many cases are either not recognized or improperly diagnosed. The chronic group can be diagnosed without much difficulty; the acute and subacute forms are the ones which may be overlooked.

The etiology in these forms of arteritis is, most likely, infection. Why and how this group of arterial diseases develops is another problem. It may be a matter of individual resistance and susceptibility and the predilection of some strains of organisms for certain tissues. This may apply particularly to the more acute forms of arteritis.

As for the other forms of inflammatory diseases, why do some individuals develop Buerger's disease and others, polyarteritis nodosa? Here again the answers are theoretical and speculative. Does it depend upon the size and location of the arteries involved? We know that in thrombo-angiitis obliterans the larger and deeper vessels are affected, that in polyarteritis nodosa the superficial arteries, both large and small, may be involved, and in the acute forms, the smaller vessels are attacked. This view, while it may be of interest clinically, is not acceptable because the pathologic findings may be general and not strictly confined to any size or location of the vessels.

We may ask: Is it possible that inflammatory arterial diseases are produced by one group of organisms varying in degree of virulence or by different strains? One is impressed by the virulence of some of these organisms. The sudden onset and rapidly developing manifestations of hemorrhages and gangrene in the acute thrombo-arteritis and the so-called cases of purpura fulminans, where gangrene and hemorrhages are extensive, with rupture of the vessels, all indicate an acute virulent organism. In periarteritis nodosa the course may be acute or subacute. Streptococci are looked upon as possible causes of the more acute forms of arterial disease; they seem to be present either in the blood stream or in some focus. Some strains, when inoculated into animals, may produce changes in the vessel walls. This experimental work is of interest. When the find-

acute thrombo-arteritis, polyarteritis nodosa and Buerger's disease (thrombo-angiitis obliterans). We are in no position to say whether these three types are produced by the same organisms operating with variations in different fields or whether we are dealing with different strains of one family group, presumably streptococci. This is a problem which will be exceedingly difficult to solve.

We have noticed that in the young the findings may be more acute, with hemorrhages and gangrene appearing early in the course of the disease. It is possible that the infectious agent may be more virulent. However, we must also bear in mind that the young are more susceptible, have less resistance, and the virgin soil of the tissues may explain the more active processes.

In polyarteritis nodosa, the disease may be acute or subacute. This form of arteritis has been more intensely investigated and in some cases, various strains of streptococci have been found.

In thrombo-angiitis obliterans, the clinical picture and behavior of the disease indicate that we are probably dealing with a less virulent organism, taking hold in various sites of the deeper vessels without exciting any startling systemic reactions, but gradually resulting in total occlusion of the vessels with periarterial inflammation. There seems to be a predilection for the deeper vessels early in its course. Veins as well as arteries are involved.

In conclusion, inflammatory diseases of the arteries do occur. They may appear in various forms. Efforts should be made to properly diagnose these conditions. Cases of purpura fulminans, idiopathic gangrene, spontaneous gangrene and Raynaud's disease with extensive gangrene should always be questioned and a thorough study of the arterial system should be made before these diagnoses are accepted. This will stimulate interest and the resulting studies may throw some light upon the etiologic processes which today seem to be cloaked in obscurity.

NOTE.—The author wishes to gratefully acknowledge the courtesies and privileges for the study of cases extended to him by Drs. Thomas McCrae, S. Solis-Cohen, J. H. Clark, director of the laboratories of the Philadelphia General Hospital, R. P. Custer and N. W. Winkelman.

glands, and a few petechial hemorrhages were observed on the eyelids and right breast. Chronic otitis media of the left ear was reported by the otologist. At the end of two weeks there were more hemorrhagic spots on the lips; the liver and spleen were barely palpable; passive congestion was noted at the base of the right lung.

By the third week the patient was considerably weaker, paler and had become delirious, with delusions of food poisoning that necessitated tube feeding. Impetigo of the left cheek developed. Examination of the eyes, which previously was negative, now showed hyperemia of the disks, with a massive retinal hemorrhage in the inferior nasal quadrant of the right eye and small hemorrhagic areas on the temporal side of the left disk; both retinae were hyperemic and edematous.

During the sixth week the delirium cleared. The spleen gradually enlarged again until it extended to the level of the umbilicus. The skin of the abdomen and legs was darkly pigmented; cachexia was extreme. Smears from the vagina contained many Vincent's organisms. In the eighth week an acute gluteal abscess developed that, on incision, drained a large amount of reddish-brown pus. During this period there was frequent bleeding from the gums and purpuric spots were noted over the lower sternum and epigastrium; the liver and spleen again receded. The lymph nodes, which had varied slightly in size from time to time, were still palpable, discrete and nonfluctuant.

The course of the patient's illness was one of progressive decline in weight and strength. The temperature varied from 95.4 to 105 F. There were two distinct afebrile periods, the first from October 12th to 16th, the second from November 3rd to 11th; with these exceptions the temperature was irregular, but would continue at times for several days at 102 F. In spite of repeated simple and nonspecific immunotransfusions, ultraviolet, x-ray and nucleotide therapy, the patient declined and died on November 19, 1932, the duration of her illness having been approximately four and one-half months.

Table 1 (furnished through the courtesy of Drs. Crocker and Valentine) condenses the more important blood findings and includes some of the therapeutic measures. Platelets (not shown in table) were 100,000 on September 1st and October 4th, and 70,000 on October 28th. Volume index was 0.7. Bleeding time, two minutes; coagulation time, three minutes. Erythrocyte fragility test showed hemolysis to begin at 0.40 per cent NaCl, complete at 0.32 per cent. Blood urea was 21 mg. per cent, sugar 87 mg. per cent and uric acid 6.5 mg. per cent. The van den Bergh reaction was negative and the icterus index 6. Blood cultures taken September 9th, 20th and 27th were negative; smears from left ear contained many streptococci and staphylococci; from gluteal abscess diplococci and streptococci and one fusiform bacillus; from vagina many Vincent's fusiform bacilli and spirillae. Fractional gastric analysis was normal. The urine was negative save for leukocytes and occasionally urobilinogen.

Lymph Node Biopsy (September 10th).—"Section through two lymph nodes is examined. The entire nodal architecture has been lost except for a remnant of one follicle. An extensive hyperplasia of reticular and endothelial elements is noted, lymphoid tissue being relatively inconspicuous. A few cosinophils are present and several multinucleated forms resembling Reed-Sternberg cells are seen. Foci of erythropoiesis are prominent. A definite sclerosing process is present, most prominent near the periphery of the nodes. From the histologic

CLINIC OF DRS. RUSSELL S. BOLES, R. P. CUSTER,
AND SIMON PROPP

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ALEUKEMIC RETICULOSIS: REPORT OF A CASE
DIAGNOSED BY STERNAL BIOPSY*

PROLIFERATIVE disease of the reticulo-endothelial system, uncommon but important, has been the source of considerable interest in the past few years. Dameshek, through case descriptions and critical reviews of the literature, has furnished an excellent picture of several of these conditions, first of "leukemic reticulosis" (monocytic or histiocytic leukemia) and next of "aleukemic reticulosis." The purpose of this paper is to describe an additional case of the latter type that was diagnosed during life, through biopsy of the sternal bone marrow, being unique in this respect to the best of our knowledge.

M. M., an Italian girl of thirteen years, was admitted to the Philadelphia General Hospital on August 30, 1932. She was well until two months before admission, when a bilateral swelling of the neck was observed, diagnosed "mumps." During the following week she grew very pale and complained of weakness; slight hemoptysis occurred. After several weeks there was purulent discharge from the left ear. Weakness became progressively more marked until the patient was quite bedfast.

On admission the patient was emaciated, dyspneic and prostrated. The positive physical findings were as follows: The conjunctivae and mucous membranes showed marked pallor; the upper lip was bleeding. There was a slight purulent discharge from the left ear. The anterior and posterior cervical, axillary, epitrochlear and inguinal glands on each side were moderately enlarged, firm and discrete. The liver edge was palpable $5\frac{1}{2}$ cm. below the costal margin; the spleen extended 2 cm. below the costal border and was tender.

Soon after admission, small nodules were felt in both parotid and mammary

* Read before the Section on Medicine of the Philadelphia College of Physicians, April 24, 1933.

levels of the sternal button, stained with hematoxylin-eosin and azure II-eosin, are examined (Fig. 140). The marrow spaces, normally 75 per cent cellular at this age, are rendered almost completely cellular through a tremendously active hyperplasia of large, pale cells with vesicular nuclei and prominent nucleoli, identifiable as cells of the general reticulum; they are seen in strands and syncytial sheets, the cytoplasm being indistinct, somewhat vacuolated and without definite cell outline; mitotic figures are relatively frequent. Occasionally a cell of this type is seen to be phagocytic and many show fine cytoplasmic processes. Where sinusoidal outlines are distinguishable, their lumina are practically occluded through hypertrophy and hyperplasia of the lining cells, resembling the chief cell

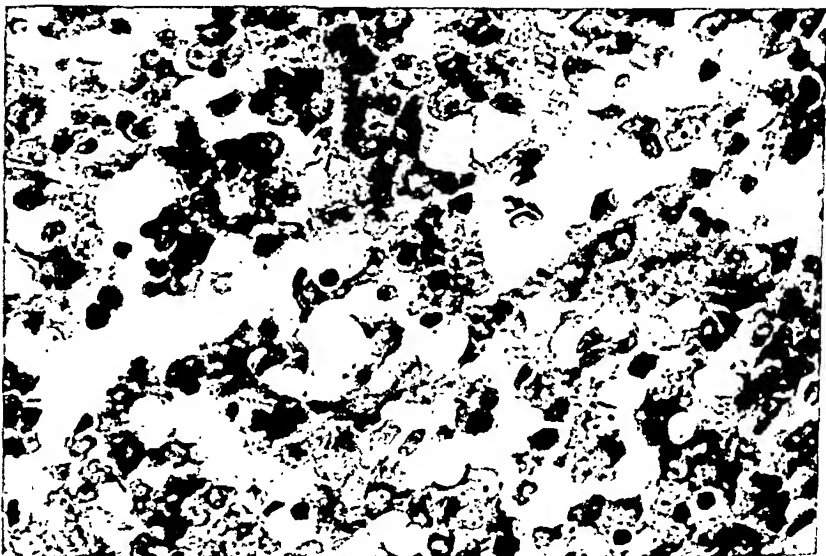


Fig. 140.—Sternal bone marrow biopsy, showing extreme reticulo-endothelial proliferation at the expense of practically all hemopoietic tissue. On this histopathologic picture the diagnosis of acute reticulo-endotheliosis was made. (From Custer, "Bone Marrow Biopsy," through courtesy of Lea and Febiger.)

type seen in the marrow. This extreme reticulo-endothelial hyperplasia has occurred at the expense of the blood-forming elements of the marrow; a few erythroblastic foci persist, and here and there one sees scattered myeloblasts, myelocytes and megakaryocytes. Diagnosis: Acute reticulo-endotheliosis (aleukemic monocytic leukemia)."

Supravital Stained Preparation of Fresh Blood (November 15th).—"Neutrophilic granulocytes and lymphocytes are readily identified by their characteristic reactions to the neutral red and Janus green. The lymphocytes are largely young forms, judging from their large numbers of mitochondria. In six preparations a single monocyte is seen; it is normal in staining reaction and motility."

Necropsy (November 19th, one hour after death).—"The subject is an ex-

TABLE 1

Date	Hemoglobin	Miles RBC	Total WBC	Multiple Index	Schilling Index	Transfusions	Myelocytes	Juveniles	Stabs	Segments	Tot. Neut.	Lymphoblasts	Large lymphs	Internod. L.	Small lymphs	Tot. Lymphs	Monocytes	Eosinophiles	Basophiles	Neutrophils on PM	Lymphocytes on PM	Normals
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
10-25	10.0	0.7	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
10-26	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
10-27	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
10-28	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
10-29	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
10-30	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
10-31	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-1	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-2	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-3	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-4	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-5	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-6	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-7	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-8	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-9	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-10	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-11	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-12	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-13	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-14	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-15	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-16	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-17	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-18	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-19	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-20	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-21	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-22	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-23	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-24	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-25	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-26	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-27	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-28	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-29	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
11-30	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-1	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-2	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-3	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-4	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-5	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-6	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-7	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-8	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-9	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-10	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-11	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-12	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-13	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-14	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-15	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-16	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-17	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-18	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-19	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-20	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-21	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-22	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-23	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-24	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-25	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-26	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-27	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-28	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-29	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-30	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc
12-31	10.0	0.8	5,000	48	5.0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	240	2310	31-600cc

Tabulated blood studies. The jagged line indicates graphically the shifts to right and left of the neutrophils. Transfusions marked with asterisk are of the nonspecific immune type, others are simple.

picture, lymphatic leukemia can be excluded (this having been the clinical diagnosis submitted with the biopsy). A definite diagnosis of Hodgkin's disease is impossible, but the node is suggestive of this condition. It is possible that a second biopsy at later date may present a more characteristic picture."

Sternal Bone Marrow Biopsy (October 31st).—"Sections through many

enlarged, although not any to great proportions, the largest being about the size of a large lima bean; they are discrete and firm, the parenchyma being homogeneous, yellowish-white and waxy. Near the head of the pancreas, and between the leaflets of the mesentery as well, nonnodal masses of tissue of the same character are noted, the largest measuring $2 \times 1 \times 0.5$ cm. Lymphoid follicles and Peyer's patches of the intestine are not prominent. The spleen weighs 328 Gm. and measures $15.5 \times 9 \times 4.5$ cm., it is large, bright red and rubbery; the pulp is not friable and does not scrape away on the knife edge. Neither follicles nor trabeculae are visible in the homogenous, jelly-like pulp.

"Hemopoietic System: Bone marrow from the sternum, rib, vertebra and femur are examined. It is pale, grayish-pink in color; the pencil removed from the femur is quite firm and meaty, homogeneous throughout. The sternum is examined at the point of biopsy; there is no evidence of inflammatory reaction, the bone defect being filled with dark red, fibrinous material.

"Endocrine System: No demonstrable trace of the thymus remains. The thyroid and parathyroids are not examined, the former not being palpably enlarged. The adrenals present normal architecture, cortical pigmentation being preserved.

"Skeletal System: An old fracture of the right elbow is noted above. There are no other gross abnormalities observed.

"Pathologist's Note: From the gross examination of this subject no disease diagnosis is apparent; it is clearly a disturbance of the hemolytopoietic system, the final judgment of which rests with the histologic examination. I see no reason thus far to alter my previous diagnosis, made from sternal biopsy, of 'acute reticulo-endotheliosis' (R. P. C.).

"Bacteriologic Studies: Cultures are taken from heart's blood, lung, spleen, femoral marrow, vagina; smears from lung, femoral marrow, pseudomembrane in vagina. (The results of these examinations were of no significance in the final analysis; all were negative save for pure culture of hemolytic streptococcus recovered from lung.)

"Histologic Examination.—All tissue was fixed promptly in Zenker-formol, sectioned at 4 micra in paraffin and stained with hematoxylin-eosin, azure II-eosin and Mallory's aniline blue.

"Heart: Beneath the epicardium there is a marked cellular infiltration, the type cell being the monocyte. The heart muscle stains palely, the fibers showing evidences of degeneration. There is no other finding of significance.

"Right Lung (Lower Lobe): There is a marked degree of congestion, all alveolar spaces being filled with edematous fluid and to lesser extent blood; occasional deposits of fibrin are noted but cellular exudate into the alveoli is inconspicuous. Bronchioles are well defined and contain edematous fluid. There is a monocyte reaction in the interstices. Many bacteria are visible within the alveoli, the majority of which are capsulated diplococci (pneumococci), the others being noncapsulated diplococci alone and in short chains (streptococci).

"Left Lung (Lower Lobe): The same picture is present here except that the intra-alveolar exudate is largely fibrinous and the cell exudate more marked, approaching actual consolidation in places; latter exudate is an admixture of neutrophils, lymphocytes and monocytes. Alveolar lining cells are very prominent through hypertrophy, hyperplasia and desquamation. Bronchioles have lost

tremely emaciated white female of fourteen years, height 150 cm., weight 54 pounds. The entire skin surface shows brown pigmentation and there are petechial hemorrhages, pin-point to pin-head in size, over the lower left chest and upper abdominal wall. The sclerae are pure white and mucous membranes and nail beds extremely pallid. There is no discharge from either ear; no ulcerative lesions are noted in the mouth or pharynx. A narrow, healed midline scar is present at the site of sternal biopsy; the left posterior cervical region is the seat of a healed incision; an umbilicated scar is present in the left gluteal region. The right elbow cannot be extended beyond an angle of 135 degrees (the result of an old fracture).

"On opening the body, blood that exudes is pale pink and watery. No subcutaneous tela remains and the muscles are wasted. There are 50 cc. of clear, straw-colored fluid in the pericardial sac, but no evidence of inflammation. Fresh adhesions are present bilaterally between visceral and parietal pleurae that are readily separable. No abnormalities are noted in the peritoneal cavity.

"Circulatory System: The heart weighs 170 Gm., aortic valve measures 5.5 cm., mitral 7.5 cm., pulmonic 5 cm., tricuspid 7.5 cm., right ventricle 0.3 cm., left 0.8 cm. The myocardium is fairly firm but of a dull, gray-brown color. There is moderate dilatation of all chambers; mural and valvular endocardium are normal. Coronary vessels show no lesions. The first portion of the aorta is the seat of a few small, bright-yellow atheromatous plaques; the remainder is clean and elastic. The peripheral vessels are normal.

"Respiratory System: The trachea and bronchi are faintly injected and contain a small amount of mucopurulent exudate. The left lung weighs 313 Gm. and the right 390 Gm. The upper lobes of each are normal; both lower lobes and the lower third of the right middle lobe are the seat of marked congestion and irregular consolidation; the cut surface of the involved tissue is granular when scraped and irregularly mottled red and gray; pus cannot be expressed from the small bronchi. The pleura is dull and translucent and covered in part by fibrinous exudate.

"Digestive System: The stomach and intestines show no lesions. The liver weighs 1800 Gm. and measures $24 \times 18.5 \times 7.5$ cm., being markedly enlarged, pale yellowish-brown and soft. On section the capsule retracts somewhat and the parenchyma bulges; blood does not exude from the cut surface, the normal markings of which are preserved. The gallbladder and bile tracts appear normal. The pancreas shows no gross lesion.

"Genito-urinary System: The kidneys are somewhat larger than normal (left weighs 208 Gm. and measures $13 \times 6 \times 4$ cm.; the right 175 gm., $11 \times 6 \times 4$ cm.), being extremely pale, grayish-yellow and soft; the capsules strip with ease leaving clean, smooth surfaces. The cut edges are rounded and the waxy, widened cortices bulge. Pelves and ureters are normal; the bladder shows no lesion of note. The ovaries are small and show no gross evidences of ovulation; the oviducts and uterus appear normal. The vagina contains a thick, fibrinous mass (some of the bulk undoubtedly due to a paste used therapeutically against the reported Vincent's infection); this is readily lifted away and no ulcerative lesion underlies it; the vagina shows no gross inflammatory lesion. The introitus and vulva are normal to gross inspection.

"Lymphatic System: Lymph node chains throughout the entire body are

prominently with the azure II; these are almost exclusively diphtheroid bacilli and diplococci alone and in short chains.

"Stomach and Ileum: Show no histologic changes of significance.

"Liver: The parenchymal cells are somewhat swollen and granular and contain small amounts of bile pigment. The Kupffer cells are more prominent than usual and occasionally one finds small clumps of proliferating cells of this type within the sinusoids. The changes here are relatively inconspicuous as compared with those in bone marrow and lymph nodes.

"Pancreas: Appears entirely normal.

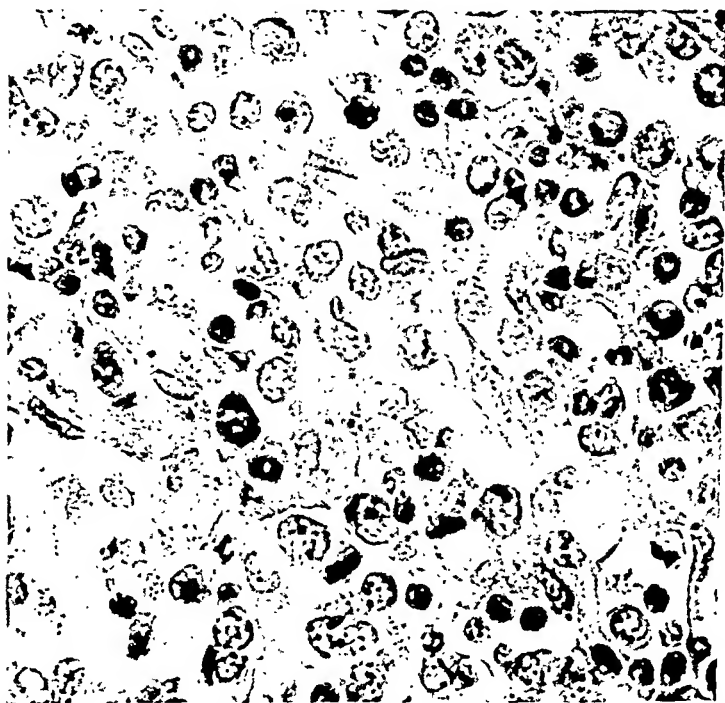


Fig. 142.—Lymph node (necropsy). High-power, showing the reticular and endothelial elements contrasted with the few remaining (darkly staining) lymphocytes.

"Lymph Nodes (Mediastinal, Para-aortic, Peripancreatic, Mesenteric, Epitrochlear): All show a uniform picture. The architecture is completely lost, no follicular remnants being visible. There is tremendous proliferation of cells of the general reticulum and sinusoidal lining, most of which lie free; latter present identical morphology to the fixed cells. Nuclei are large and vesicular, being irregularly round, oval or indented; the perinuclear membrane is sharp and clearly defined with small chromatin granules attached thereto. The nucleus is rather spongy, due to the interlacement of exceedingly fine chromatin network; nucleoli may or may not be present. The cytoplasm is irregular in

their epithelial lining in part and contain fibrinopurulent plugs. The bacterial content is not nearly so prominent as in the right lung.

"Spleen: Capsule is normal. The general architecture has been lost, follicles being hardly identifiable. There is an extreme degree of congestion and the pulp is comparatively empty. The cells that remain are a uniform admixture of histiocytes, lymphocytes and plasmacytes, the former predominating and showing an occasional multinucleated form. Sinuses are indistinct; where identifiable, their lining cells are hypertrophic and resemble morphologically the large clear cells found free within sinuses and pulp. There is no increase in interstitial tissue. A considerable amount of hemosiderin is present, both free and phagocytosed.



Fig. 141.—Lymph node (necropsy). Low-power, showing complete loss of architecture and seeming invasion of the thickened capsule by proliferating histiocytes.

"Adrenal: Presents no histologic variation from normal.

"Kidneys: Each presents the same histologic changes. Glomeruli appear normal; tubular epithelium, especially convoluted portions, is swollen, granular and the nuclei indistinct. The interstitial tissue is the seat of an extensive reticulo-endothelial proliferation (infiltration?), separating many of the tubules and being most prominent in glomerular peripheries. The organs are markedly congested.

"Vaginal Pseudomembrane: This is composed of fibrin, the mass being laminated. Beneath the free surface are myriads of bacteria that stand out

GROSS ANATOMICAL DIAGNOSIS

Acute reticulo-endotheliosis (?)

Anemia: Emaciation.

Skin: Thoracic and abdominal petechiae. Pigmentation.

Aorta: Juvenile atheroma (slight).

Heart: Myocardosis.

Lungs: Catarrhal tracheobronchitis. Passive congestion with edema and hypostatic pneumonia (right middle and both lower lobes). Fibrinous pleuritis.

Spleen: Splenomegaly.

Adrenals: Normal.

Kidneys: Toxic nephrosis (marked).

Urinary Bladder: Normal.

Internal Genitalia: Fibrinous vaginitis (mild).

Gastro-intestinal Tract: Normal.

Liver: Hepatomegaly. Toxic hepatitis.

Lymph Nodes: Hyperplasia (marked).

Bone Marrow: Hyperplasia (extreme).

HISTOLOGICAL DIAGNOSIS

Acute reticulo-endotheliosis (aleukemic reticulosis).

Myocardosis. Subepicardial round-cell infiltration.

Catarrhal bronchitis.

Passive congestion with edema and hypostatic pneumonia.

Reticulo-endothelial hyperplasia.

Lymphoid hypoplasia. Passive congestion.

Normal.

Toxic nephrosis. Reticulo-endothelial hyperplasia (infiltration?). Passive congestion.

Fibrinous vaginitis.

Normal (stomach and ileum).

Kupffer cell hyperplasia. Toxic hepatitis.

Reticulo-endothelial hyperplasia.

Lymphoid hypoplasia (replacement).

Reticulo-endothelial hyperplasia.

Myeloid hypoplasia (replacement).

Comment.—During the early period of observation lymphatic leukemia was considered; this was based on the history, generalized lymphadenopathy, hepato- and splenomegaly and hemorrhagic manifestations, with relative (but not actual) lymphocytosis. This diagnosis was excluded by the findings in the lymph node biopsy. Neutrophils disappeared from the peripheral blood on five different occasions (when one considers that the differential count was based on one hundred cells, it is a question whether such findings are dependable); this led some to think of agranulocytic angina (Schultz's syndrome) but the extreme degree of anemia and thrombocytopenia, the age of the patient and the clinical course were opposed to such diagnosis.

amount and for the most part vacuolated, often drawn out into long, delicate processes that do not take the aniline blue stain. Occasional small multinucleated forms are seen, resembling Reed-Sternberg type. A number of the cells contain phagocytosed erythrocyte fragments and nondescript cell debris. This predominant cell type stands out in sharp contrast to the remaining intermingled lymphocytes.

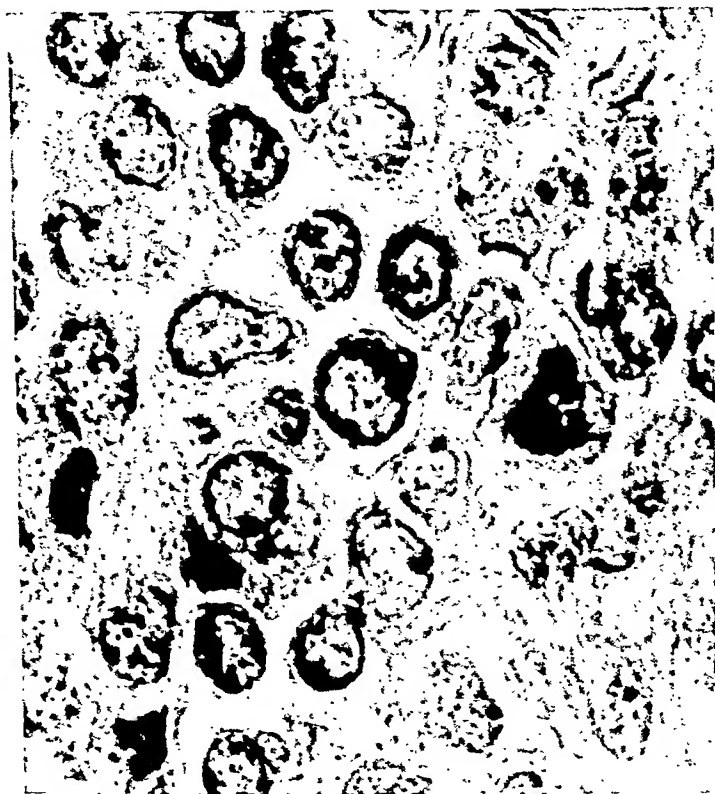


Fig. 143.—Femoral bone marrow. All cells in the field are of histiocyte type. Cell detail is clearly shown, *i. e.*, large, vesicular nuclei, vacuolated cytoplasm with processes. Four of the cells contain phagocytosed debris.

"Bone Marrow (Femur, Sternum and Vertebra): All show a uniform picture except that the vertebra contains a slight amount of persistent hemopoietic tissue. Aside from this the marrow spaces are completely filled with cells of the reticulo-endothelial type described above. Instead of the syncytial formation seen in the sternal biopsy (about three weeks before) the majority of cells have rounded up and appear as free forms (Fig. 143); their morphology is otherwise the same."



CLINIC OF DR. MYER SOLIS-COHEN

JEWISH AND MT. SINAI HOSPITALS

QUININE IN THE PNEUMONIAS OF INFANCY AND CHILDHOOD

CHEMOTHERAPY is seldom employed in the pneumonias. Indeed modern text-books rarely so much as refer to this method of treatment, although for over a century the favorable influence of quinine upon the course of pneumonia has been noted by many competent observers, including Corrigan, Gibson, Sée, Liebermeister, Binz, Aufrecht, Cahn-Bronner, George B. Wood, Austin Flint, DaCosta, Jacobi, Solomon Solis-Cohen, and Kolmer. Carefully controlled observations upon adults have shown a mortality of 9.6 per cent in 1000 cases of pneumonia treated with quinine as compared with 20 per cent in 2000 controls which were similarly treated in every way except that they received no quinine. During the last twenty years another cinchona derivative, ethylhydrocuprein or optochin, has also been employed, but the clinical results with its use have been less favorable than those with quinine.

Quinine and optochin have been shown to be specifically bactericidal to pneumococci both *in vivo* and *in vitro*. Administered to human beings and to the lower animals, they appreciably increase the pneumococcal activity of the blood and reduce the resistance of pneumococci to it, thus enhancing the immunological destruction of the latter. Part of the curative effect of cinchonics in pneumococcus infections probably is to be ascribed to their stimulating influence on leukocytosis and on the phagocytic activities of the leukocytes for pneumococci. Autolysis of pneumococci, shown by Lord and Nye to occur at the crisis, when the lung has reached a high degree of activity, has been found by Ash and the writer to occur in a more alkaline hydrogen ion concentration, and hence at an earlier period,

in the presence of quinine. The circulation of quinine in the infiltrated lung has been suggested as playing some rôle by interfering with the mechanism of the disease.

For twenty years the writer has been administering quinine to infants and children with pneumonia, having treated adults with it since 1906. He does not give them optochin (marketed at one time under the trade name of numoquin) for the reasons that it is more dangerous and less efficacious than quinine; it favors the development of optochin-fastness, which Ash and he have shown may develop very quickly as the result of only one or 'two days' exposure to the drug; it has to be given for three days, while quinine frequently does not have to be given longer than six to twelve hours; during the whole period of its administration the only food and drink allowed is milk, which always has a tendency to produce tympanitis; and it is useful only in pneumococcic pneumonia and in the lobar variety.

The writer's clinical results with quinine have been very favorable, with an extremely low mortality in both lobar and bronchopneumonia, except in cases of true influenzal pneumonia and of a peculiar form of acute interstitial pneumonia, not mentioned in the text-books, and in patients first seen after the occurrence of cardiac failure.

The most pronounced effect of quinine in pneumonia is upon the toxemia, which may subside though the temperature be unaffected. This is shown in the changed appearance of the patient and especially in the prevention of myocardial damage, even with persisting fever, so that convalescence frequently is shortened to a few days. Some observers speak of the impression one gets as if quinine diminishes the effect of the bacterial products in the blood stream. Others believe that the drug acts solely on the toxin of pneumonia circulating in the body, rendering it harmless, and that consequently it represents a sort of antitoxin against the poison of the diplococcus. The fact that enormous amounts of quinine administered during the height of pneumonia fail to produce cinchonism is regarded by many as furnishing evidence that quinine and the pneumonia poison must neutralize each other.

A common result of quinine treatment is a shortening of the duration of the pneumonia. Flint, Bartholow, Cahn-Bronner, and Solomon Solis-Cohen state that they have arrested or aborted a lobar pneumonia with quinine. Frequently by administering a large dose of quinine at the onset of the disease the writer has been able to abort both lobar and bronchopneumonia, especially the grippal form of the latter.

Reduction of the fever has been observed by practically all who have administered cinchonics in pneumonia, the majority regarding the fall in temperature as a direct result of the neutralizing of the toxemia and not as due to any antipyretic action. The rapidity with which the fever is checked is believed by some to have a relation to promptness in beginning quinine treatment. In most of the writer's cases quinine caused a reduction of the fever. This sometimes was brought about promptly, but in many instances was considerably delayed. After the first drop the temperature remained down in only a small minority of cases, as a rule rising again. Quick recrudescence of fever and apparent refractoriness or resistance of fever to quinine does not impress the writer, as it does some others, as significant of the ineffectiveness of the drug in the particular case, but rather as an indication for further and more vigorous treatment with larger doses and more prolonged administration.

A favorable effect from quinine upon the general symptoms of pneumonia has been noted by many observers, Cahn-Bronner regarding it as above all the most striking result from the administration both of quinine and of optochin. In most of the writer's cases an improvement in the patient's general condition followed the administration of quinine.

The physical signs were unaffected by quinine in some of his cases. In others they disappeared rapidly after its administration. As a rule the spread of the disease was checked. Among the different clinicians there is no general agreement as to the effect of quinine on the physical signs.

The prevention of complications is generally regarded as another effect of quinine therapy. In the writer's cases heart failure, empyema, septicemia, and meningitis have been rare,

which accords with the experience of others. Otitis media, however, did not seem to be prevented in his patients nor was mastoiditis such a rare complication.

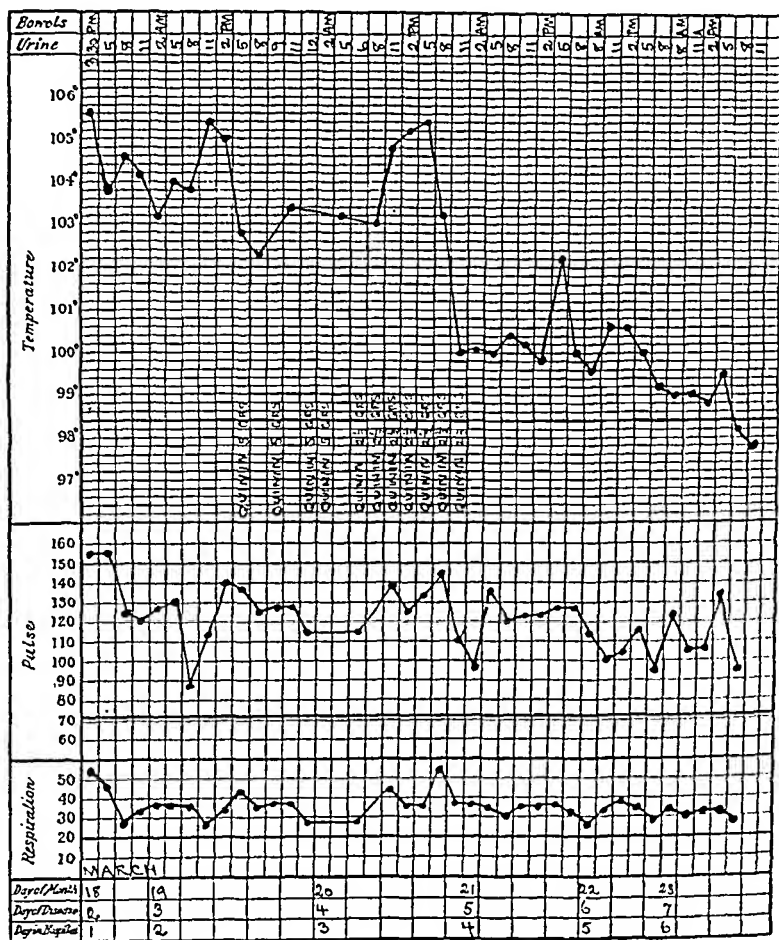


Fig. 144.—H. M., aged twenty-two months. Lobar pneumonia, involving right upper lobe. Complication bilateral chronic mastoiditis. Leukocytes 29,400. Received $37\frac{1}{2}$ grains of quinine in thirty hours.

The method of quinine administration that the writer prefers is the oral, which is easy and safe and seems to give sufficiently prompt results. He administers quinine dihydrobromide in capsules to children who can swallow them. For others the

salt is dissolved in syrup of yerba santa or in Lilly's coco-quinine (each drachm of which already contains 2 grains of quinine sulphate). When the stomach is intolerant, quinine and urea hydrochloride is given intramuscularly or in a suppository.

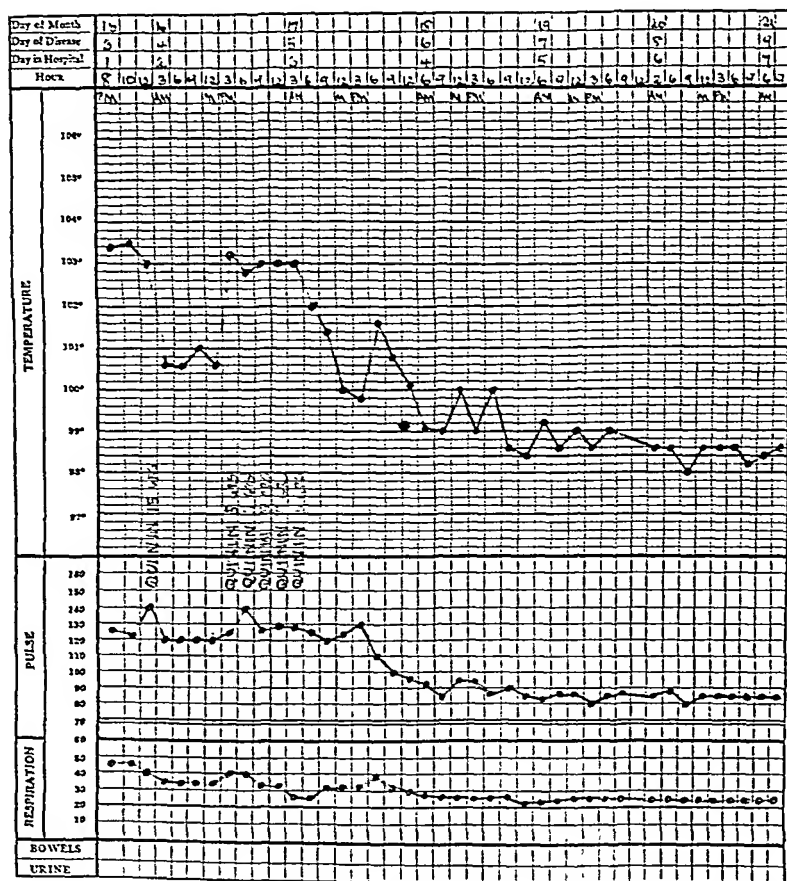


Fig. 145.—E. J., aged six years. Lobar pneumonia, involving right middle and lower lobes. Leukocytes 22,300. Received 15 grains of quinine in one dose and subsequently 25 grains in five doses at three-hour intervals.

The intramuscular method of administration is employed in very serious cases and when the patient is first seen late in the disease, a 50 per cent solution of quinine and urea hydrochloride being used. Sloughing and tissue necrosis, however,

may be produced if the solution enters the subcutaneous tissue. To prevent this the writer uses a long needle, which is washed off and filled with sterile distilled water (never normal salt solution) after the quinine solution has been drawn into the syringe.

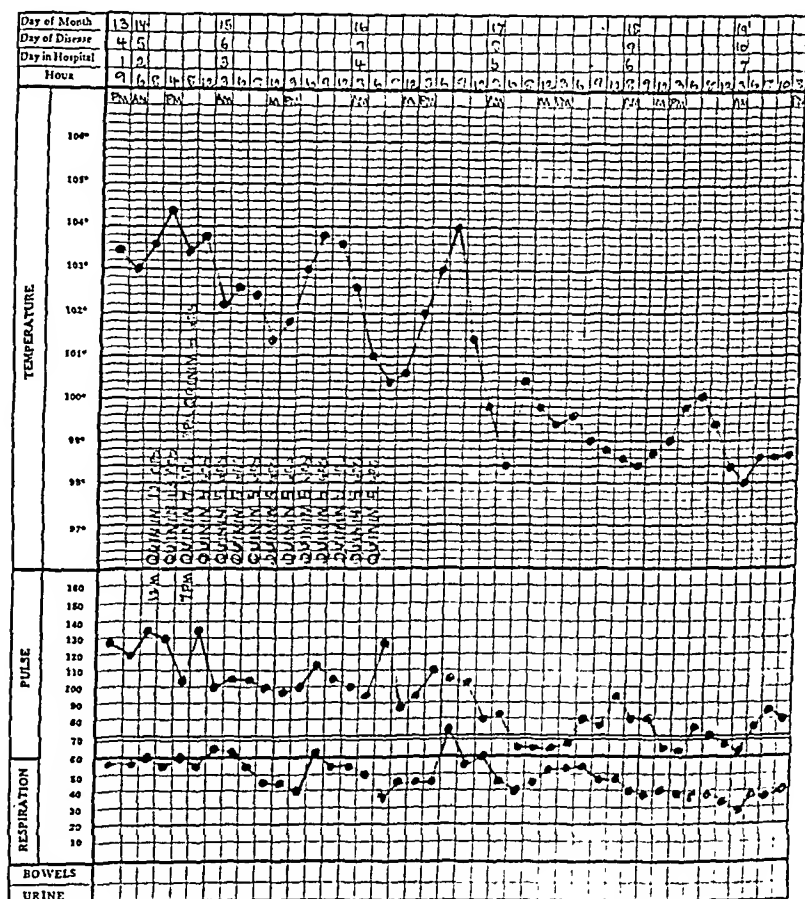


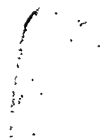
Fig. 146.—J. H., aged five years. Bronchopneumonia. Leukocytes 17,700. Received 91 grains of quinine in three days.

Before withdrawing the needle from the muscle, the syringe is thoroughly emptied, detached from the needle—which is left *in situ*—filled with air or sterile distilled water (never normal salt solution), again attached to the needle, and its contents expelled.

The rectum and anus may become irritated when many quinine suppositories have to be inserted, as well as when the drug is given by enema, a favorite method of Jacobi. Although some deny that quinine is absorbed from the rectum, the writer's experience, together with reports from competent observers, convinces him that it is.

The writer administers the drug at three-hour intervals if at such time the temperature is above 100.5 F. The dosage is based upon the age, size and development of the child and the type, stage and severity of the disease, being a matter for clinical judgment in the individual case. In general an infant six months of age or younger is given one or two doses of 10 or 5 grains, followed by doses of 5 or $2\frac{1}{2}$ grains. During the second half of the first year $7\frac{1}{2}$ to 15 grains are given at the first two doses and $2\frac{1}{2}$ to 5 grains thereafter. A patient sixteen years of age or older receives an initial dose of 30 grains, followed by another dose of the same amount and subsequent doses of 15, 10 or 5 grains. Between the ages of one year and fifteen years the doses are graded accordingly. Rarely do such doses administered during the height of the fever give rise to cinchonism or deafness.

The accompanying temperature charts (Figs. 144-146) of infants and children with lobar pneumonia and bronchopneumonia, receiving quinine treatment, illustrate the different pictures presented by patients treated with this drug.



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sensation of both eyeballs. This became progressively worse and in a few weeks she observed a red spot on the conjunctiva at the inner canthus of the left eye. Within the next year both eyes became, as she expressed it, "pink" in color and a stringy secretion developed. There was severe itching and burning, especially at night. The lids gradually became adherent to the bulbar conjunctiva and the vision was diminished.

She, at this time, in May, 1929, consulted Dr. William T. Shoemaker who made a diagnosis of ocular pemphigus with destruction of the conjunctiva and symblepharon. On examination, June 14, 1929, he noted bullae formation on the bulbar conjunctiva of the right eye. Adhesions apparently formed rapidly although the patient could see fairly well, and could read until three months ago.

About six weeks ago she developed what she described as indigestion, *i. e.*, discomfort in the epigastrium, distention and "gas" associated with difficulty

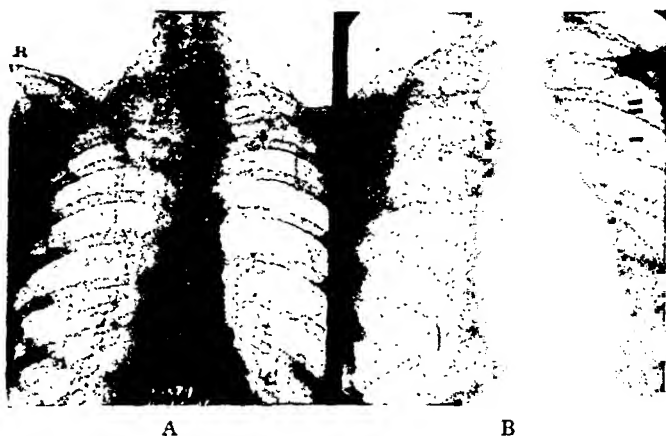


Fig. 148.—A, Anteroposterior roentgenogram of the esophagus showing stenosis at the level of the suprasternal notch; B, no evidence of stenosis, 1/11/33.

in swallowing solid food. The difficulty in swallowing has become progressively worse until at the present time she can take only small quantities of liquid. She has had two similar attacks of "indigestion" since the changes in the eyes developed. One attack occurred two years ago and one three months ago. Neither attack was as severe as the present one, but she has some dysphagia.

She has had one period of fr [unclear] but no frequency but some difficu [unclear]

She has lost about 25 pounds

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CLINIC OF DR. FRIEDA BAUMANN

FROM THE DEPARTMENTS OF MEDICINE AND APPLIED THERAPEUTICS, THE WOMAN'S MEDICAL COLLEGE OF PENNSYLVANIA

ESSENTIAL SHRINKAGE OF THE CONJUNCTIVA (OCULAR PEMPHIGUS) WITH INVOLVEMENT OF THE MUCOUS MEMBRANES OF THE NOSE, THROAT AND LARYNX AND STENOSIS OF THE ESOPHAGUS. (DETAILED TREATMENT OF A CHRONIC DISEASE OF UNKNOWN ETIOLOGY)

ESSENTIAL shrinkage of the conjunctiva has been most frequently described by the ophthalmologists as ocular pemphigus.

We are able not only to show you a typical picture of this rare disease, but also to illustrate the practice of the art of



Fig. 147.—Note the symblepharon and partial ankyloblepharon of both eyes.

medicine in a case where the lack of knowledge of the disease with which we are confronted calls on all our resources and skill in the application of therapeutic measures.

Case Abstract.—M. K., aged sixty-one, was seen first November 21, 1931, in an extreme state of malnutrition and dehydration, supposedly suffering with cancer of the esophagus. She stated that four years ago she noticed a dry

and larynx with retraction and scarring. Stenosis of the esophagus cannot be demonstrated today.

The history which you have just heard describes well the clinical signs and symptomatology.

In the earlier manifestation, the disease may be very difficult to diagnose as it may be confused with the more or less acute inflammatory or infectious diseases of the eye.

The later stages, in cases without evident lesions of the other mucous membranes, must be differentiated from the sequelae of trachoma, and diphtheria, and from the scarring and shrinking resulting from strong acid or alkali burns. The anamnesis is therefore most important.

The largest number of cases have been observed in Germany and Austria and over fifty years ago the pathologic picture was described in detail by the German ophthalmologists. Because of the rarity of the disease even the most experienced ophthalmologists seeing thousands of cases have had very little opportunity to observe more than 1 or 2 cases of the disease over any length of time. By all observers the picture has been described most typically in those cases having lesions only in the conjunctiva, or those with simultaneous involvement of the mucous membrane alone, that is in those cases not influenced by any marked disturbance of the skin.

In the cases described in detail after long observation, vesicles or bullae of the conjunctiva were only occasionally noted. As you just heard, in our case, Dr. Shoemaker, earlier in the disease, observed the presence of bullae only on one visit. I have no other record of this observation being made by other physicians who have seen this patient.

The fact that blebs are not more frequently noted is explained by most ophthalmologists as being due to the delicate anatomical structure of the epithelial layers of the conjunctiva. However, as in our case, circumscribed red areas which later become covered with grayish exudate frequently appear. These spots slowly progress to cicatrization, and shrinking of the adjacent conjunctiva takes place. The retrotarsal folds disappear and adhesions are formed between the bulbar and palpebral

of occasions she has deprived herself of food, and twice during pregnancies—the second and third—she was unable to eat because of the distaste for many foods, although she had no nausea and no vomiting.

During the last pregnancy, although the patient's diet was better, the skin was very dry and the fingers cracked about the nails.

Physical examination showed the patient as a very nervous, emaciated, dehydrated white woman with the following positive findings: Weight, 75 pounds. Temperature 98 F. Pulse 80. Eyes: Left eye: Lids are adherent entire length. Right eye: Symblepharon is practically complete except for the circle of the cornea. The patient can see light. There is trichiasis of both lids. Mouth: No teeth. Throat: Some localized congestion of the hard palate. Deep ulcers, surrounded by inflamed areas and scar tissue over both hard and soft palate and on the anterior pillar of the left tonsil. Tenacious mucoid exudate in the pharynx. Tonsils: Imbedded, atrophic. Nose: Septum markedly deflected to the right anteriorly and to the left in the ethmoid region. There is ulceration anteriorly and the mucous membrane is markedly congested. Small mixed tumor of the left parotid gland. Chest: Hyposthenic type. Heart and Lungs: No evidence of pathology. Abdomen: Scaphoid type. Rather marked fulness and distention below the umbilicus. Right kidney palpable. Skin: Dry, scaly, with definite lesions of dermatitis herpetiformis over the arms and scapular region. Rectal and vaginal examination showed no evidence of involvement of mucous membrane.

Dr. Joseph V. Klauder concurred in the diagnosis of ocular pemphigus and considered it a distinct entity and entirely different from that pemphigus which consists of skin lesions and better termed "essential shrinkage of the conjunctiva."

Roentgenographical studies revealed a benign stricture of the esophagus at the level of the suprasternal notch.

Laryngoscopy and esophagoscopy showed the following picture: "The epiglottis was deeply congested, infiltrated and showed a few tiny blebs on the upper area. About 2 cm. below the cricopharyngeus there was a tight stricture of the esophagus. The stricture seemed to be about 3 cm. in length. The membrane was not ulcerated and the walls did not seem to be infiltrated. The stenosis was dilated and a feeding tube was introduced."

The feeding tube was left *in situ* for five days. When it was removed, x-ray studies of the gastro-intestinal tract were made and no evidence of the stricture of the esophagus was apparent. Visceroptosis, redundancy and dilatation of the colon were noted.

All clinical pathologic studies were essentially negative except for a moderate microcytic anemia, and gastric achlorhydria.

DISCUSSION

The diagnosis is not difficult in the stage in which we see our patient. There is, as you have noted, shrinkage of the conjunctiva, with practically complete symblepharon, ankyloblepharon and trichiasis. Also there are definite lesions of the pharynx

There is considerable difference of opinion in the literature concerning the actual nature of this disease. The majority of the ophthalmologists seeing these cases consider them a manifestation of pemphigus. This is probably due to the fact that blisters of the conjunctiva had been observed and that various cutaneous lesions were frequently associated with the condition.

There was also, at the time pemphigus of the conjunctiva was first described, much confusion and discussion concerning the diagnosis of pemphigus of the skin. Diseases which have since been identified as not belonging to the pemphigus group were included largely because at some time in the course bullae or blisters were noted. Pemphigus of the skin may be associated with bulbous and inflammatory lesions of the mucous membranes of the mouth, throat and eyes. The involvement may be marked and the severe cases terminate in death, but milder cases may go on to healing.

In reviewing many of the recorded cases of essential shrinkage of the conjunctiva or ocular pemphigus, some grave symptoms suggestive of gastro-intestinal tract involvement were noted, and a rather large percentage showed definite lesions of the mucous membranes of the upper respiratory tract with shrinkage similar to that of the conjunctiva.

This shrinkage, the typical lesion of the disease we are discussing, is not any way similar to the lesions of any of the types of skin pemphigus described, by the dermatologists. The course is chronic and may be of many years' duration. No cases have been recorded as improved or cured, although quiescent or arrested periods have been noted.

The disease has been observed and treated largely by the ophthalmologists and we are indebted to them for the careful clinical descriptions.

However, a study of the reported cases suggests that the disease is one which should be more carefully studied by the internists. The ophthalmological picture is obviously only one manifestation of a general disease.

conjunctiva. The conjunctiva becomes whitish and cloudy and striae similar to those of trachoma form. This process, however, as noted by the first careful observers, begins in the fornices and the lower bulbar and palpebral conjunctiva, in contradistinction to the lesions of trachoma. As the disease progresses, the conjunctival sac is completely obliterated, and adhesions form causing a more or less complete symblepharon, and ankyloblepharon as you have observed in this case. There is a loss of tears due to atrophy of the lacrimal sac. Trichiasis also frequently occurs. As in our case, the cornea is usually the last area which becomes adherent to the palpebral conjunctiva and the patient may be able to discern light and shadow through the lids.

The etiology is unknown. That a general toxemia due to some unknown factor is present is only probable.¹ The presence of a toxemia in essential shrinkage of the conjunctiva does not necessarily identify this condition with pemphigus.

If a toxemia is present, this may be of exogenous origin or be derived from altered metabolism due to some change in organic function. In our patient, because of the dietary history, we thought a deficiency might be present. We have found nothing during our observation of this case to verify this possibility.²

The association so frequently of similar lesions of the mucous membranes, especially those of the upper respiratory tract, with the conjunctival shrinkage suggested to some observers a neurotrophic origin. The local, or possible peripheral lesions of essential shrinkage of the conjunctiva, are of a definite progressive chronic nature, and trophic changes have been noted in the nails and hair. However, there is no neuropathologic evidence to bear out this theory.

¹ The high index recorded by the Pels-Macht phytopharmacological test in this case supposedly points to the presence of a toxic substance in the blood. There is a high index in pernicious anemia. Sufficient studies of other diseases of known etiology have not yet been recorded to give the test great significant value.

² Dr. E. V. McCallum (personal communication) has seen no analogous condition in animals in dietary deficiency experiments.

There is considerable difference of opinion concerning the actual nature of this disease. the ophthalmologists seeing these cases as manifestation of pemphigus. This is probably due to the fact that blisters of the conjunctiva had been observed and that cutaneous lesions were frequently associated.

There was also, at the time pemphigus was first described, much confusion and difficulty in the diagnosis of pemphigus of the skin. It has since been identified as not belonging to the group of diseases which were included largely because at some time blisters or bluish lesions were noted. Pemphigus of the skin with bulbous and inflammatory lesions of the skin, and of the mouth, throat and eyes. The involvement of the skin and the severe cases terminate in death, while the mild cases go on to healing.

In reviewing many of the recorded cases of the conjunctiva or ocular pemphigus, one finds symptoms suggestive of gastro-intestinal disease, and in many cases noted, and a rather large percentage of the cases show shrinkage of the mucous membranes of the upper lip similar to that of the conjunctiva.

This shrinkage, the typical lesion of pemphigus, is not any way similar to that of skin pemphigus described, by the fact that the disease is chronic and may be of many years' duration. It has been recorded as improved or cured, and arrested periods have been noted.

The disease has been observed by ophthalmologists and we are inclined to accept their clinical descriptions.

However, a study of the recorded cases of the disease is one which should be made by internists. The ophthalmologists have described a manifestation of a general dis-

TREATMENT

There is no known curative or specific treatment. To a large degree we are in the same position as Franke when over thirty years ago he said: "The treatment must be confined to relieving the grievances of the patients."

We, however, have considerable advantage, in that advance in methods of treatment and refined technic in mechanical procedures have given us a better therapeutic armamentarium on which to call.

On first seeing this patient we were confronted with a woman unable to take solid food, showing marked malnutrition and dehydration.

She was placed on frequent feedings of high carbohydrate, *i. e.*, glucose solutions and fruit juices. An oil enema followed by a 2 per cent sodium bicarbonate enema was given. Then enteroclysis of isotonic saline solution was instituted.

As soon as stenosis of the esophagus was diagnosed, an esophagoscopy was done and a Jute tube passed. Through this, concentrated high carbohydrate and balanced protein feedings were given. The fat content of the diet was kept low because of the gastric hypo-acidity.

Protein was obtained largely from milk, egg albumin and whole grain cereals.

We were prepared to give a small blood transfusion merely as a supportive measure, but the patient responded so promptly this was not necessary. As noted, in five days we were able to remove the tube and give feedings by mouth. Since she had no teeth, all coarse foods were sieved or ground.

Because the patient gave us a positive history of badly balanced diets, a high vitamin diet was planned. She was exceedingly nervous and irritable, and also showed evidence of intestinal stasis and ptosis. Therefore large quantities of both factors of vitamin B were given, at first as vitavose, 2 drachms three times daily, later in the form of yeast. Vitamin C was provided by orange juice, tomato juice and the juices of all the cooked vegetables. Butter, cream and egg yolk were given in

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the literature. E. Franke wrote a monograph in 1900. He reported 5 cases of his own and made very detailed abstracts of all the cases (102) since the first was reported by White Cooper in 1858. After careful evaluation of the material he suggested that the condition be carefully studied apart from pemphigus and that the name pemphigus be dropped and the affection be designated shrinkage of the conjunctiva with vesicle formation.

Groenow, who has written an excellent description of pemphigus, makes the following comment: "The clinical picture given by Alfred von Graefe as essential shrinkage of the conjunctiva is not definitely to be identified as pemphigus notwithstanding the many cases cited."

In presenting a case three years ago at the Dermatological Society, Philadelphia (December, 1930), Dr. Klauder identified it as essential shrinkage of the conjunctiva and said: "There are only 4 cases on file among many thousands of cases of disease of the eye at the Wills Hospital."

In conclusion we wish to call attention to the fact that there is considerable evidence suggesting that so-called "ocular pemphigus" is a distinct lesion of the mucous membranes and is not manifest either clinically or pathologically by lesions characteristic of pemphigus. We feel, moreover, that it will aid in further study of these cases to designate them as essential shrinkage of the conjunctiva and mucous membranes with vesicle formation until an etiologic factor is determined.

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The relationship of this fact to the age period of infectious mononucleosis appears suggestive. In addition to the free lymphoid cells, a reticular stroma exists in lymphoid structures. It consists of two types of cells: (1) Reticular cells of large size and stellate in form with pale, oval nuclei of the histiocyte class capable of phagocytic properties; (2) reticular syncytium with undifferentiated mesenchyme without phagocytic qualities which however can be transformed into reticular cells and lymphocytes. Even the cells lining the sinus wall can be interpreted as flattened reticular cells. According to Maximow's conception monocytes may arise from the lymphocytes in lymph sinuses and small blood channels of the liver, spleen and bone marrow. Cunningham, Sabin, and Doan, however, hold to the theory of a specific origin of monocytes from monoblasts in the spleen and bone marrow. Plasma cells also arise from small- and medium-sized lymphocytes by differentiation of the individual cell without mitosis. It is apparent at this point that, according to these expressed conceptions, lymphoid tissue contains within itself nearly all the components, actual and potential, necessary to build up even the complex pathologic picture of Hodgkin's disease. It is also obvious that the redundant and confusing pathologic terms, such as "epithelioid cells" and "endothelial cells" in the description of lymphogranuloma could well be discarded.

Under ordinary circumstances the stimulus initiated by bacteria, toxins or chemicals produces only temporary reactive changes. It is highly probable, though not subject to proof, that in certain individuals there is in consequence set up an irremediable progressive hyperplasia analogous to malignancy in other structures of the body. Though it pertains equally to the other lymphoblastomas this hypothetical element of bacterial provocation has been particularly applied to Hodgkin's disease. For example the localization in the cervical group of nodes has been attributed to predisposing infections arising in the teeth, tonsils, nasopharynx and sinuses. It has been frequently noted that respiratory infections of the influenza group have preceded the onset of Hodgkin's disease of the cervical or mediastinal

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A DISCUSSION OF THE LYMPHOBLASTOMAS

IN the consideration of the diseases grouped for convenience under the broad term of "lymphoblastoma" we are at the outset confronted with the varying and conflicting theories of lymph node physiology as well as with the difficulties inherent in our conception of neoplastic diseases in general. Despite the fact that we are delving into a highly controversial field, it is worth while to consider briefly some of the salient features of lymphoidopoiesis as exemplified in the contributions of Maximow and others. The primary follicles of the lymph nodes and malpighian nodules of the spleen appear as dense darkly staining areas composed mainly of medium- and small-sized lymphocytes with a small proportion of large lymphocytes. The small lymphocyte represents the mature phase of this series and is the normal lymphocyte of the blood. It develops mainly by mitotic division of the medium-sized lymphocyte. The large lymphocyte apparently is a temporary form and represents an off-shoot in the developmental stage. The follicle or primary nodule of lymphoid structure as a rule contains a central lighter staining area—the germinal center or secondary nodule. The appearance of these areas varies considerably in their active and resting phase. The medium-sized lymphocytes are found in large numbers in this area and exhibit mitoses particularly in the active phase. To some, these areas represent the chief site of lymphoid cell proliferation; other observers regard them only as reaction centers to bacterial and other irritants.

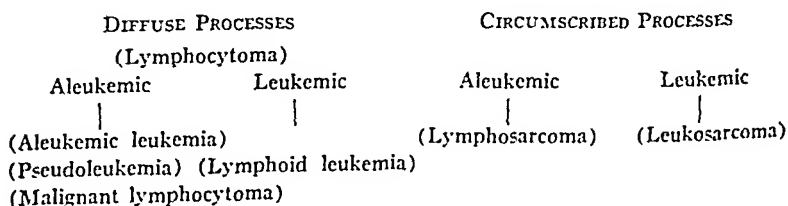
It is curious to note in passing that according to some investigations, they diminish markedly after the third decade.

as follicular lymphoblastoma because it appears to be the malignant phase of follicular lymphadenoma which is ordinarily benign. The comparatively long duration of this disease and the peculiarity of its giant-size secondary nodule seem to establish it as a separate entity. One can theorize that the mild degree of malignancy is due to retention of the identity of the follicle as a unit despite the abnormal proliferation of its germinal center.

The remaining lymphoblastomas are all essentially proliferations of certain cellular structures in a diffuse manner with obliteration of the normal structure of the lymph node. They may involve a single cell type almost exclusively or a combination of cells; this latter pattern may be in some respects due to multipotential properties of stem cells and produces the composite picture of lymphogranuloma.

LYMPHOBLASTOMAS OF THE LYMPHOCYTE GROUP

The many and various clinical types of processes involving the lymphocyte upon closer analysis resolve themselves into four main groups depending on, first, whether they are diffuse and universal proliferations of the lymphoid series, or circumscribed, infiltrative and invasive processes with strong resemblance pathologically to sarcoma; secondly, whether they are accompanied by leukemic or aleukemic blood pictures. It is apparent that there can be no hard and fast distinction among such groups and that inevitably types will merge by degrees into one another. Arranged schematically this division would appear as follows:



In the group of aleukemic lymphocytomas the lymph node structure is altered or destroyed by diffuse proliferation of cells

nodes. In an analogous manner one cannot fail to note the onset of some of the abdominal types of Hodgkin's disease after infections which for want of a better term have been designated intestinal forms of influenza. The fact that in many localities mesenteric lymphadenopathy has been found during outbreaks of this infection, appears to lend emphasis to this possibility.

The relationship of tuberculosis to Hodgkin's disease has been a matter of dispute for some time. Ewing's classic and frequently quoted pronouncement that in New York "tuberculosis follows Hodgkin's disease like a shadow" leaves much to individual interpretation with a wide field for speculation. It is understandable that with the wide prevalence of tuberculosis it should be among the most frequent of the various bacterial irritants which underlie the beginning hyperplasia of the lymphoid structures and which later may take on the malignant features of Hodgkin's disease. The recent work of Sabin, Doan and Forkner has indicated the precise fractions of the tubercle bacilli which are responsible for the various features of the histopathology of tuberculosis. Of these the phosphatide fraction A-3 is of particular interest in this discussion since it produces the most massive reaction toward epithelioid cells and epithelioid giant cells. Other fractions such as the purified wax and glycerides produce marked stimulation of general connective tissue with potentialities for fibroblasts, clasmotocytes, plasma cells and fibrous tissue. Transferring these changes in terms of lymph node cytology it appears evident that cells characteristic of lymphogranuloma can be specifically stimulated by fractions of the tubercle bacilli. The possibility that Hodgkin's disease is a manifestation of avian tubercle bacillus infection has been suggested by the work of L'Esperance. In a critical review of avian tubercle bacillus infections, Branch suggests further experiments in apes before this relationship can be established. Leaving the rather nebulous phase of this topic the practical details of morphological classification and description may be approached. At one end of the scale in the varying degree of malignant proliferation of lymphoid structure should be placed the process described by Rosenthal and his collaborators

The small mature or nearly mature lymphocyte of the blood smears of chronic lymphoid leukemia is characterized by a nucleus slightly indented on one side, occupying most of the cell. The chromatin of the nucleus is dark and composed of angular or wedge-shaped masses when stained by some of the Romanowsky modifications. In ordinary fixed preparations no nucleoli are noted though they can be detected in supravital preparations stained with brilliant cresyl blue. The cytoplasm contains azurophilic granules while mitochondria (chondriosomes) brought out by Janus green in supravital preparations are less in number than in the immature forms or lymphoblasts. Size alone should not be depended upon as an indication of immaturity of lymphocytes but in a general way the so-called "lymphoblasts" are larger, the nucleus is composed of dotlike bits of chromatin, a heavy nuclear membrane is present and nucleoli are readily apparent by ordinary stains; the cytoplasm is more basophilic, mitochondria greater in number and azurophilic granules less than in mature lymphocytes. Peroxidase stains are negative for granules. Blood platelets which may be normal in the early stages of the disease fall later due either to bone marrow invasion or to the effects of radiation therapy. At this stage hemorrhagic manifestations will occur. Necrotic lesions of the mouth occur in acute types and in the terminal stage of subacute and chronic types and appear to be related to the disappearance of granular cells. The cutaneous manifestations are particularly distinctive. They consist of multiple nodular infiltrations or papules over the face, neck and trunk. The occurrence of these lesions may aid in distinguishing lymphoid from myeloid leukemia when the cells in the blood smears are poorly differentiated.

The following case report illustrates a type of subacute lymphoid leukemia with skin manifestations.

Case I.—H. P., male, aged sixty-four. Nodular infiltration of skin, lymphadenopathy and massive splenomegaly. Total leukocyte count 490,000, with approximately 95 per cent medium-sized immature lymphocytes. Duration of the disease presumably nine months. Blood smear (Fig. 149) indicates the character of cells and is fairly representative of instances of subacute lymphoid leukemia.

of the lymphoid series in many lymph node chains and the spleen; small mature lymphocytes if predominant are associated with a rather prolonged course, exhibiting only low-grade malignant features and with little invasive tendency, immature larger or lymphoblastic cells with a more acute and malignant course. There is no leukemic blood picture. The gradation of this process into that of true leukemia was afforded by the study of several cases in which increase in cells of the lymph follicles and cords with pyknotic and wedge-shaped nuclear chromatin was noted at biopsy during exacerbation. At this time lymphocytes with the same characteristics appeared in the blood in small numbers together with moderate increase of apparently normal lymphocytes. A precise term in instances like this is obviously a matter of individual opinion and for all practical purposes not even necessary provided there is a fairly clear conception of the pathologic process and its effect on the clinical course.

LYMPHOID LEUKEMIA

This disease may also involve lymphocytes of the small mature variety in which case a prolonged course is noted lasting over a period of years, occasionally up to ten years. However when the increase predominatingly affects various stages of the medium-sized lymphocyte—the so-called “lymphoblasts” of most hematological descriptions—the course is acute or sub-acute. The more embryonal or less differentiated is the cell, the more acute is the course of the disease. The disease appears in a group of nodes subsequently involving other chains and in many instances all accessible groups appear enlarged. The follicles usually fuse with the lymph cords due to the massive lymphoid cell hyperplasia. The fundamental resemblance of the disease to malignancy appears to be supported by the experiments of Richter and MacDowell which indicate that the transmissible leukemia of mice depends upon the viability of the inoculated leukemic cell. The studies of Furth and Strumia also point to the neoplastic nature of transmissible mouse leukemia and are of particular interest in the recognition of initial aleukemic lymphadenosis in these animals.

appear in the blood the condition merges into that of leukemia or leukosarcoma. However, even in typical instances a few lymphoblasts may be found in blood smears as exemplified in the following case:

Case II.—J. E., male, aged thirty-nine. Diagnosis of mediastinal mass confirmed by x-ray. Large numbers of lymphoblasts found in aspirated pleural fluid (Fig. 150). Leukocyte count 5300 with a few lymphoblasts noted in the blood

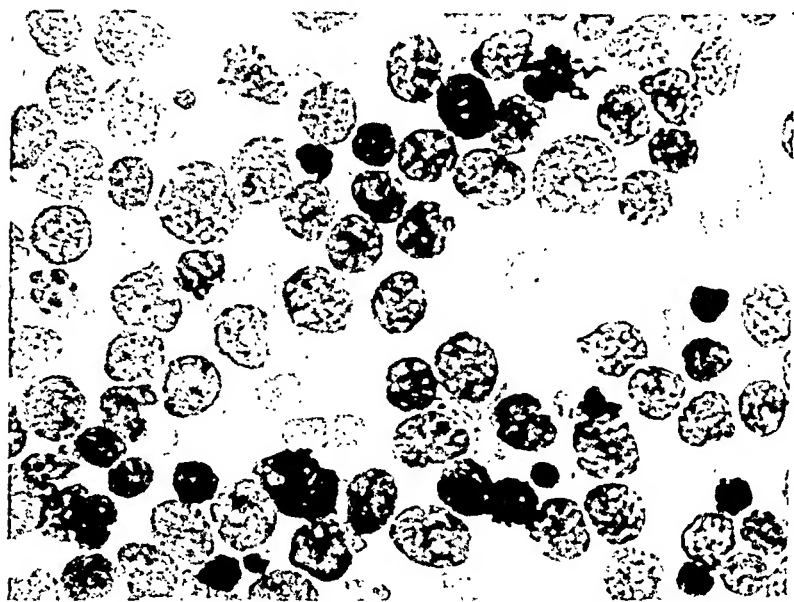


Fig. 150.—Lymphosarcoma. Smear from pleural fluid of Case II. Variation in size of cells mainly of lymphoblastic type; large stippled chromatin; nucleoli and vacuoles noted. ($\times 1050$.)

smears. Autopsy (Dr. Gouley) revealed a cartilaginous mass occupying the entire mediastinum; metastatic lesions in kidneys. Tumor is composed of cells similar to those found in the pleural fluid.

The following case report illustrates a variety of factors operating to alter and distort the usual course of a lymphoblastoma of this group:

Case III.—L. D., a medical student, aged thirty-two (service of Drs. Pfahler and Leopold). Diagnosis of lymphosarcoma made on biopsy from an enlarged left supraclavicular node. The patient's father died at the age of forty-one of a lymphosarcoma originating in the same area. During his medical course the

LYMPHOSARCOMA

The delineation of this syndrome is usually credited to Kundrat who described a disease originating in a group of lymph nodes with typical features of malignancy and locally invasive character. True metastases are formed which may be both by lymphatics and by blood stream. It apparently owes its malignant nature to the involvement of less differentiated lymphocytes such as medium and large lymphocytes of the class of lym-

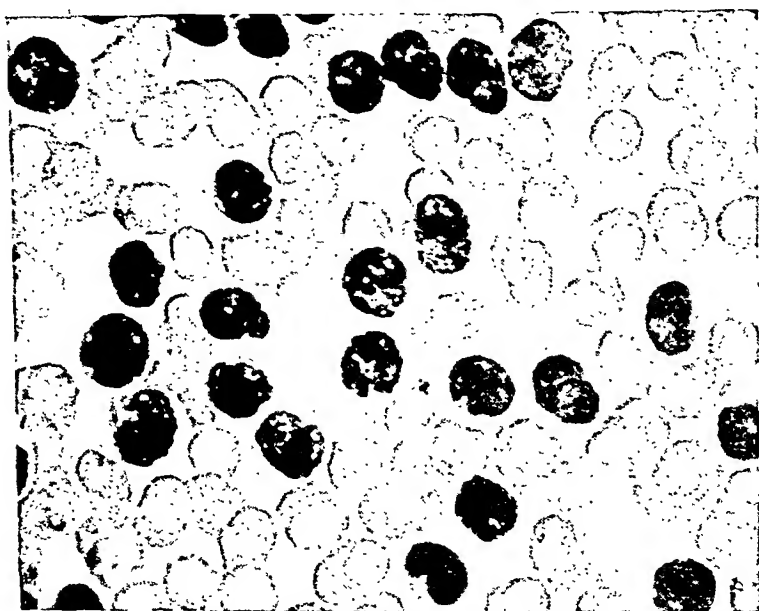


Fig. 149.—Blood smear of subacute lymphoid leukemia, Case I. Medium-sized lymphocytes of lymphoblast type with heavily stippled nuclear chromatin, dense nuclear membrane; some cells show indented nuclei. ($\times 1330$.)

phoblasts. Though the reticulum cell is placed in this group according to some classifications, in this discussion reticulum cell sarcoma will be grouped with the reticulum cell changes of Hodgkin's disease. Lymphosarcoma has a predilection for involvement of a particular group of lymph nodes or a restricted area such as in cervical, mediastinal, retroperitoneal and gastrointestinal types. It is thought that some of the mediastinal types originate from thymus tissue. When the abnormal cells

Though in his illustrations they resemble lymphoblasts and some are depicted in mitotic division, he designates them "atypischer einkerniger leukocyten." There is ample evidence to include immature lymphoid cells of other varieties in cases conforming to the same general combination described above. This view has been discussed in a description of a case of leukosarcoma by Flashman and Leopold. The possibility of thymic origin has been considered in the mediastinal cases though the existing doubt as to the histogenesis of thymic parenchyma has prevented general acceptance of this hypothesis.

The following case history is representative of this syndrome:

Case IV.—J. T., male, aged twenty-two. Mediastinal mass noted on x-ray examination. Leukocyte count varied from 120,000 to 156,000 with approximately 95 per cent immature medium-sized lymphocytes showing tendencies to amitotic division.



Fig. 151.—Leukosarcoma, Case IV. Anterior view showing entire mediastinum encased in tumor; incision through anterior aspect reveals chamber of left ventricle.

patient had done considerable research work on dogs involving fluoroscopical technic. About four months before admission he suffered with what seemed to be Vincent's angina and received several doses of neoarsphenamine. Three weeks before admission he first noted the enlarged nodes before the left clavicle. At this time a leukopenia was noted with a total leukocyte count of 3000 and 60 to 80 per cent lymphocytes. After the original node was excised for examination he received x-ray treatment over the affected area and surrounding structures. The blood picture throughout showed a steady drop in red cells, hemoglobin, leukocytes and platelets indicating universal bone marrow failure. In most of the blood smears lymphoblasts in small numbers were noted. Patient succumbed September 12th, fifteen days after admission, despite frequent transfusions.

At autopsy (by Dr. Case) the outstanding findings were massive hemorrhages into the tissues of the posterior mediastinum pressing upon the aorta. Extensive hemorrhage of the esophageal walls was present. Bone marrow showed no evidence of regeneration. Though the lymph nodes in various areas showed hyperplasia of the germinal centers there was no visible evidence of lymphosarcoma anywhere in the body.

Discussion.—There was present in this patient an unusual number of factors which may have influenced the hematopoietic structures. There was a history of hereditary susceptibility as indicated by the singular coincidence that his father succumbed to the same disease and in the same region. He had received trauma to bone marrow function by three possible agencies—x-ray exposure, neoarsphenamine and the effects of the tumor itself. It is possible that the mouth lesions which appeared to be due to Vincent's angina may have been due to beginning granulopenia. Due to these circumstances, the clinical course was so altered that a form of aplastic anemia caused the death of the patient before local recurrences appeared.

LEUKOSARCOMA

This term has been applied to a process exhibiting locally sarcomatous invasion with a leukemic blood picture consisting of cells analogous to the predominating cell of the tumor mass. It appears to be a transition form of lymphosarcoma with the added blood picture of leukemia. The lymphoid tissue does not share universally in the process as it does in leukemia. The typical cells according to Sternberg's original description were large amitotic lymphocytes containing either sharp indentations in the nuclei or two nuclei; he described the nucleus as pale with a honeycomb-like appearance containing two or more nucleoli.

to occur in younger individuals. In so far as the histopathology is concerned, the duration of involvement in a particular chain of nodes is reflected in the varying microscopical picture, *i. e.*, section of lymph nodes enlarged for a longer period will show more fully developed and characteristic combinations of cells with more fibrosis and greater numbers of Reed cells than those chains recently enlarged.

Regardless of the area which the process first involves, as a rule other groups of lymph nodes eventually enlarge, though occasionally the disease may remain restricted to one area or structure. The latter circumstance gives rise to reports of mediastinal, abdominal and splenic Hodgkin's disease and so on. This extension of the disease though accepted clinically as a natural sequence of events is nevertheless not without its theoretical problems. Is a toxic agent transmitted by lymphatics or is there a general blood distribution of the unknown factor? These possibilities are invoked by those who consider the disease to have only a locally invasive power not typical of the metastatic activity of malignancy. It may not be out of place to apply the hypothesis of Murphy in his experiments on the filtrable agent of chicken sarcoma. This thought presupposes that the unknown inciting agent derived from tumor cells may confer upon other specific normal cells of similar derivation the metaplastic character of tumor cells which then are transferred in turn to descendent cells. He believes a similar property is responsible for the specific types of pneumococci and other phenomena of specificity of cells and bacteria. He has coined the term "transmissible mutagen" to designate this hypothetical factor. It is a matter of conjecture what bearing this has upon the problem of lymphoblastoma.

Without any intent to go into the details of the histopathology, it can be first stated that in a general way the disease is one involving the reticulum cells and the still less differentiated reticular syncytium; that a particular cell may outstrip others in growth, as for example in reticular cell sarcoma; that the continued presence of the original bacterial incitant may possibly modify the histopathology as suggested in the discussion

Autopsy (Dr. Gouley): A large solid mass was present in the chest filling the entire mediastinum and encasing the pericardium; the great vessels are



Fig. 152.—Case IV. Section of mediastinal mass. Diffuse proliferation of lymphoid cells with character described in autopsy report. ($\times 240$.)

entirely embedded in the mass. Metastatic nodules in the kidneys. Microscopical sections indicate tumor mass is composed of medium-sized and large round cells with hyperchromatic nuclei (lymphoblasts).

PROCESSES INVOLVING THE RETICULUM (RETICULUM CELL SARCOMA, HODGKIN'S SARCOMA, HODGKIN'S GRANULOMA)

Hodgkin's disease or more precisely malignant lympho-granuloma is world wide in its distribution if available literature is a criterion and though a racial predisposition is not pronounced, it is somewhat more common in the white race. This fact may be due in part to differences in available statistics. Heredity as a rule is of negligible importance. All observers agree in its greater preponderance in the male sex in the proportion of 2: 1 or even more. The greatest incidence is in the third to fourth decade of life though cases are described in children and in the aged. There is a greater tendency for the acute types

Case V.—E. S. L., female, aged twenty-one (service of Dr. J. C. Doane). Inguinal lymphadenopathy followed by generalized lymph node enlargement. Intermittent septic-like temperatures and death in six weeks. Biopsy sections of epitrochlear node examined by Dr. Levine were described as follows:

Section of tissue shows destruction of germinal centers and lymph follicles. Lymph channels are also absent. The glands showed a network fibrillar in character. In the meshes of this there is a proliferation of reticular cells with fairly clear cytoplasm. Some of these contain granules. Cells of the lymphocytic series are also noted; some of the nuclei are hyperchromatic. A few eosinophils and scattered polynuclear leukocytes are present throughout the section (Fig. 153).

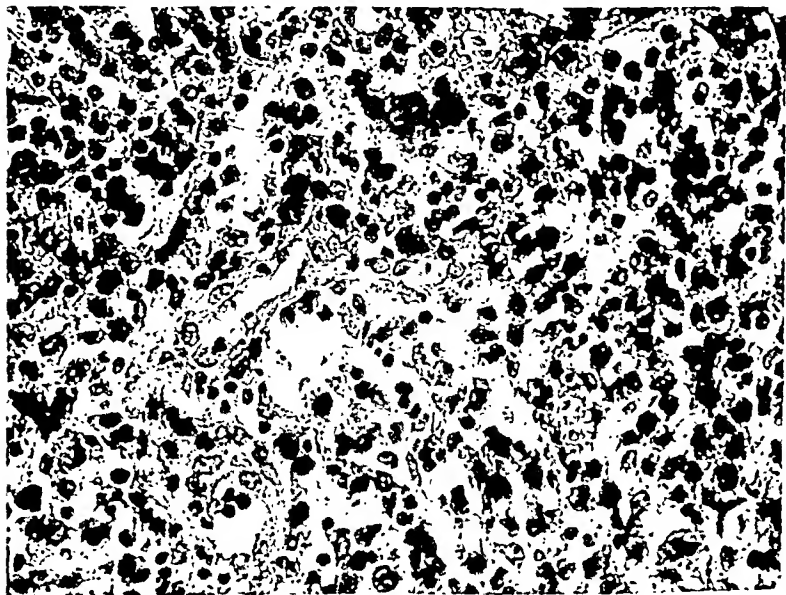


Fig. 153.—Section of node of Case V, showing changes indicative of acute Hodgkin's disease. Fibrillar network with hyperplastic reticulum cells destroying normal architecture. None of the cells, however, has progressed to multinucleated stage. Leukocytes described in text do not show well in illustration. ($\times 560$.)

Comment.—The atypical character of the histopathology may be taken as indicating the earliest phases of acute Hodgkin's disease. These changes have no opportunity to assume a fully developed character because the patient succumbs to the disease before this occurs. The presence of neutrophils at so early a stage helps to confuse the picture with an inflammatory process particularly with the association of Pel-Ebstein fever.

of tubercle bacillus fractions. All these are again conditioned by the age and resistance of the patient, duration of the disease and of the particular group of nodes under examination, not to mention effects of radiation and other forms of therapy. While in the early stage there may be a reactive increase in the lymphocytes, in the main the proliferation of the reticular cells gradually destroys the normal architecture of the node with the gradual lessening and disappearance of the lymphocytes. The greatest aid in the microscopical diagnosis of the disease is the multinucleated cell derived apparently from a large reticular cell. The nuclei of these cells vary in number from two to ten approximately. Though the characteristic grouping of the nuclei is in the center of the cell, when they are greater in number they may be arranged in arciform manner at the periphery of the cell similar to the Langhans' giant cell. The true foreign body giant cell is exceptional. Considerable doubt exists as to the nature of the neutrophilic and eosinophilic leukocytes in the lesions. Some contend that they have been attracted to the area by some chemotactic influence while others believe they arise locally by some form of myeloid metaplasia. The protagonists of the latter theory believe that the lack of comparable blood changes in these patients supports this view. This does not appear to be convincing if, on the contrary, neutrophils can be demonstrated in a fixation abscess in patients with extreme granulopenia at a time when scarcely any polynuclear cells can be found in blood smears. Again admitting on physiologic evidence mentioned at the beginning of this discussion that the undifferentiated stroma can undergo myeloid transformation, it appears likely that more intermediate forms would be present. Occasionally the eosinophilic infiltration has been noted as an accompaniment of skin lesions though here blood eosinophilia is usually present. Plasma cells are also frequently found; fibroblasts or reticular fibrils appear early and are therefore not necessarily a sign of attempt at fibrous healing.

Atypical variants particularly in the category of acute Hodgkin's disease are well illustrated by the following summary:

tures of interest are the changes in the leukocytes, platelets and blood calcium after splenectomy.

To continue the description of the blood changes in Hodgkin's disease, it is usual to find a secondary or hypochromic

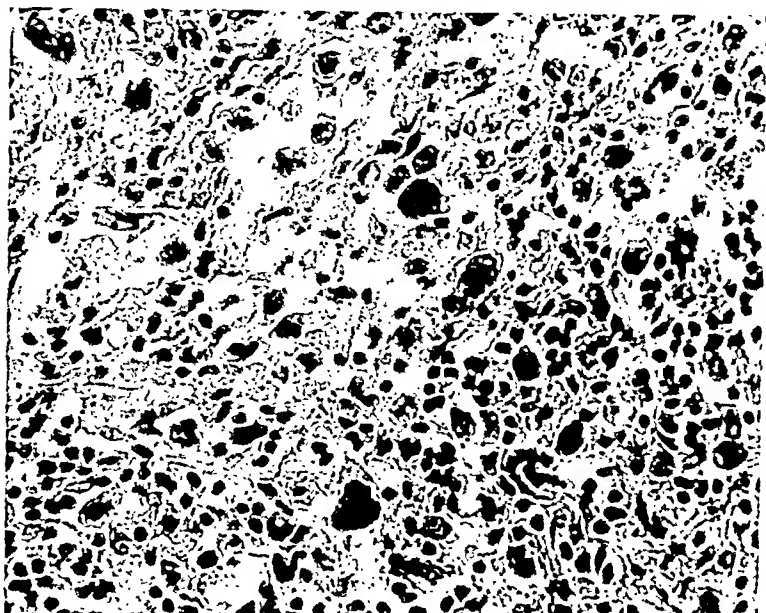


Fig. 154.—Case VI. Hodgkin's disease with many features of reticulum cell sarcoma. Marked and diffuse reticular cell proliferation with enlarged forms assuming beginning multinucleated characteristics. Considerable fibrocytosis and almost complete absence of lymphocytes. ($\times 560$.)

anemia gradually becoming more severe due to nutritional changes, involvement of the bone marrow by the process or due to the unknown toxic material responsible for these changes in malignant disease generally.

SUMMARY

There are obviously a number of phases of lymphoblastoma which could not be included in the scope of a presentation so fragmentary. It suffices however to indicate the need for elucidation in the physiology and pathology of lymphoid tissue with a better correlation of the two; greater simplification in classify-

BLOOD CHANGES

In some respects the blood is a mirror of what is going on in the lymph node despite the fact that in the individual case at one particular time the diagnostic value may be little. As an example, the moderate lymphocyte increase in the early stages may be synchronous with the first reactive stages in the lymph node; later when the lymphocytes disappear from the follicles, lymphopenia is apt to be the rule. In a like manner leukocytosis and eosinophilia may reflect the presence of the cells in the lesion. An increase in monocytes is probably characteristic and in several instances I have observed fluctuations characterized by decreases during improvement induced by x-ray treatment and increases during exacerbations. In addition the blood picture may be influenced by various factors such as involvement of the spleen, bone marrow, presence of skin lesions, and cachexia. The peculiar influence of splenic involvement in modifying some of the hematological and chemical features of Hodgkin's disease is apparently not emphasized sufficiently, particularly as a cause of leukopenia, thrombopenia and possibly hypercalcemia with decalcification. This point is brought out in the following case history:

Case VI.—F. S., male, aged twenty-nine. Splenic enlargement, moderate lymphadenopathy and evidences of decalcification in pelvis and long bones of lower extremities. Red blood cells, 2,700,000; hemoglobin, 54 per cent; white blood cells, 3800; platelets, 151,000. Splenectomy was done because of possibility of Gaucher's disease followed by rapid rise in platelets, leukocytes and red cells. Blood calcium dropped by stages from 17.2 mg. on the day before operation to 15 mg. two weeks after operation and to 12 mg. about two months later. He died on a readmission in December, 1930, with a hemolytic streptococcus infection of the pleural cavity.

At autopsy (by Dr. Case), a retroperitoneal tumor was found with extension to the parietal peritoneum, pleural sacs, metastasis to the ureters, lymph nodes of inguinal region, portal, mesenteric peribronchial and mediastinal regions.

In the affected lymph nodes the lymphoid tissue was largely replaced by large reticular cells, many of which were multinucleated, mitoses frequent; a typical section is shown in Fig. 154.

Comment.—The process here is a transitional form between reticular cell sarcoma and typical Hodgkin's disease. The fea-

ing the lymphoblastomas with the thought that they represent similar processes of various components which merge into one another at times with insensible gradations. The fundamental problem of causation, however, must await the ultimate outcome of investigation in neoplastic diseases in general.

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there is also a relationship between cholecystitis, especially the calculous type, and angina pectoris. A number of observers have called attention to this but the profession at large seems to be unaware of this association because the standard works on medicine either fail to mention or do not stress the fact that there may be a relationship between the two. Graham states, "we know of suspected cases of angina pectoris receiving complete and permanent relief following cholecystectomy after it had been determined there was a pathologic gallbladder." Willius reports that in his cases of angina pectoris associated with gallbladder disease, 52 per cent of the patients were definitely benefited so far as the angina was concerned by removal of the gallbladder; some of his patients never had another anginal attack after the operation. Judd states that he does not hesitate to do a cholecystectomy on any case of angina pectoris provided the patient is adequately prepared for operation. Because of this relationship between gallbladder disease and heart disease and especially because of the association between calculous cholecystitis and angina pectoris I advised cholecystectomy for this patient.

On account of his poor cardiac condition some of the staff thought he might not be able to survive the ordeal of a major surgical procedure and they counselled against operative intervention. A compromise was effected in that it was decided to limit the operation to the less time-consuming and less serious procedure of removal of the stones through cholecystostomy.

Of course some one may say that the attacks of angina in this case were merely the referred pains of biliary colic. We know that in some cases gallstone colic is referred substernally and to the precordium and may give the impression that we are dealing with angina pectoris just as we know that in some cases of angina pectoris the pain may be referred to the upper abdomen or right hypochondrium and may simulate perforated peptic ulcer or acute pancreatitis or cholelithiasis. The failure of analgesics to relieve his pains and the relief experienced by the use of the xanthine group of drugs, I believe, rules out referred gallstone colic.

CLINIC OF DR. JOSEPH G. WEINER

JEWISH HOSPITAL

THE RELATIONSHIP OF CHOLELITHIASIS TO ANGINA PECTORIS

THE subject of my presentation today is an adult white male, aged forty-three. When I first saw him about four months ago I found him in a typical attack of angina pectoris. He was sitting bent forward in bed with his left hand over his precordium; there was an agonized expression on his ashen-gray features which were covered with perspiration, and with difficulty in speech he complained of intense substernal and precordial pain and implored for relief. He had had a number of such attacks within the previous few weeks. Prior to his admission, he had been under treatment at home and had been confined to bed for about three weeks without any improvement in his condition. In addition to his attacks of angina he had a systolic apical murmur and at times a rough systolic murmur heard best over the midsternum. The area of cardiac dulness was within normal limits. He had also a poor myocardium—the heart sounds were very weak and extrasystoles were present on many occasions. He was very dyspneic, orthopneic at times, he had a slight edema of his ankles, a few râles could be heard at the bases of his lungs, there was a cyanotic tinge to his lips and fingernails and he was of necessity confined to bed. Blood pressure averaged 135 systolic over 85 diastolic.

At this time he was on analgesics and sedatives for the relief of his pains, without any effect. Previous to that he was on digitalis to improve his myocardial efficiency, but the attending physician at that time had to discontinue it because of gastric irritability, anorexia and couple rhythm.

In addition to his cardiac pathology he had a calculous cholecystitis as evidenced by positive microscopy of his B fraction. We found cholesterol crystals and calcium bilirubinate pigment in his biliary aspirates and the presence of these two elements is almost always pathognomonic of stone. He also had the negative shadows of stone on his cholecystogram.

It was evident that the present treatment was doing very little to improve the patient's condition. It was also obvious that unless we did something additional beside bed rest we could never hope to send him back to his home as a well person and that he was therefore doomed to be a cardiac invalid.

For the relief of his anginal attacks I placed him on coronary vasodilator medication, so that on the use of theophylline, $1\frac{1}{2}$ grains t.i.d., he experienced relief and comfort from his distressing substernal pains.

We are all acquainted with the fact that there is an association between gallbladder disease and degenerative changes in the myocardium. What seems to be less well known is that

disease and angina pectoris may occur together as two separate and distinct clinical conditions. However the presence of cholecystitis, especially the calculous type, may so accentuate and aggravate a coexisting angina pectoris, whatever its underlying pathology may be, that operative intervention upon the gallbladder should be considered. The presence of angina pectoris should be no contraindication to surgical intervention. Butler and others at the Peter Bent Brigham Hospital made a study of 414 patients with heart disease who underwent 494 surgical operations with the significant finding that there were only 28 unexpected deaths. Of these, 41 operations were performed on 35 patients having angina pectoris with 3 unexpected deaths. A large number of these unexpected deaths can properly be regarded as accidents that occur in the natural course of heart disease, or of surgical operations. For example a patient with angina pectoris who has never had any surgical operation may during his life develop a fatal attack of coronary thrombosis. The conclusion reached in their study was that in most types of heart disease the surgical risk is not appreciably greater than in the normal person.

Conclusions.—Gallbladder disease, especially the calculous type, and coronary disease may coexist. Rest and medical treatment alone may fail to improve such hearts. Patients who are invalided by such an association may be restored to a state of usefulness by gallbladder surgery. Timely surgical intervention may preserve the heart from irreparable damage. The presence of angina pectoris should not deter one from recommending surgical intervention.

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He had also a moderate degree of jaundice. The quantitative van den Bergh reaction varied between 1.9 and 3.4 van den Bergh units and his icterus index between 20 and 38 units. The van den Bergh reaction was never direct. Bile was never present in the urine. Urobilinogen was present in the urine in dilution of 1:10 (Wallace and Diamond method). His blood count was normal: Red blood cells, 4,000,000; hemoglobin, 90 per cent. He had a leukocytosis varying between 10,000 and 18,000 with a normal differential count. Fragility of red cells was normal. Blood cholesterol was 130 mg. per 100 cc. Blood Wassermann negative. Blood chemistry—normal values. The liver edge was palpable 1 cm. below the costal margin. Liver function studies: The bromsulphthalein test using a 2-mg. dose showed 5 per cent retention at the end of thirty minutes. The galactose tolerance test was normal. The temperature curve was generally at a normal level with a few short excursions up to 99.4. The electrocardiogram showed probable coronary sclerosis.

Three weeks after admission he was operated upon under spinal anesthesia. A number of stones were removed by cholecystostomy. Following his surgical convalescence he has made a splendid clinical improvement. He has not had any attack of anginal pain since. Whereas previous to the operation he was intensely dyspneic and bed-confined he is now ambulant, has very little dyspnea, the ankle edema has disappeared and there are no râles at the bases of his lungs. I do not wish to give the impression that he is cured of his heart disease because he still has his diseased gallbladder wall within him, but the splendid clinical improvement, the improved morale, the fact that he is ambulant has justified the operative intervention.

Angina pectoris is not a clinical entity; it is only a symptomatic manifestation of a number of varied organic and functional states. Cardiac pain may occur in many conditions in which the heart is not primarily the seat of trouble. We must look upon angina merely as a symptom and in the search for its cause we may occasionally find unsuspected gallbladder disease. The gallbladder is enervated by sympathetic fibers arising in the solar plexus around the celiac axis and by medullated fibers from the left pneumogastric. The exact mechanism in the production of angina pectoris has never been definitely established. In its relationship to gallbladder disease angina probably occurs as a result of a reflex phenomenon through irritation of the vagus. That there may be no anatomical basis for anginal attacks has been shown by the absolutely negative findings in many cases that have come to autopsy.

I do not wish to intimate that when calculous cholecystitis and angina pectoris coexist that a cholecystectomy will relieve every case of angina. It is not to be forgotten that gallbladder

siness, stupor, coma and death. Headache is uncommon unless hypertension is present, and hypertension is unusual in such cases.

A less frequent condition in which high degrees of nitrogen retention are encountered, not due to renal insufficiency, is that associated with prerenal deviation of water, such as excessive vomiting due to pyloric or intestinal obstruction. In such instances, the clinical features include dehydration, hypotension, slow shallow breathing, subnormal temperature, occasionally mental confusion and delirium, and convulsions which are tetanic in character. The convulsive seizures are due to an alkalosis, which is the result of the hypochloremia. The therapeutic indication is the restoration of the body fluid and salt. This may be accomplished by the parenteral administration of sodium chloride solution.

The cause of the cerebral manifestations in primary arterial hypertension is still indefinite. The associated signs of kidney disease, such as albuminuria and casts, led to the assumption that the symptoms were uremic in origin. This erroneous impression has been corrected since the advent of blood chemistry in the study of kidney disease. As has been indicated above, blood nitrogen estimations reveal normal or nearly normal values. Likewise function tests fail to indicate renal impairment of a degree sufficient to cause the symptoms. In a few reported cases, no evidence of renal damage could be demonstrated by the available tests. However, as the disease involves the general vascular tree, the kidneys do not escape; but such kidney changes as may be present are the result and not the cause of the condition. The disease is usually terminated by cerebral apoplexy or cardiac failure; renal impairment may be a contributing factor, but as the primary cause of death it is rare. Hypertension plays an important part in the etiology. The condition is rarely, if ever, seen in the absence of high blood pressure. Furthermore, the symptoms of cerebral irritation promptly subside after the reduction of vascular tension. The evidence seems to indicate that the hypertension is secondary to widespread arteriolar constriction. That the smaller vessels

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HYPERTENSIVE ENCEPHALOPATHY SIMULATING BRAIN TUMOR

ACUTE cerebral disturbances due to essential hypertension are encountered not infrequently. The onset of this syndrome may be sudden, although the patient often exhibits various premonitory symptoms for several days such as headache, vertigo, drowsiness, insomnia at night, failing vision, nausea and vomiting. The attack may closely resemble the convulsions of epilepsy or eclampsia, and end in coma. The coma, partial or complete, may follow progressive drowsiness without convulsions. Transient paraplegia or hemiplegia may occur. Various combinations of the above symptoms have been observed, with or without convulsions or coma. The blood pressure is always elevated and the blood nonprotein nitrogen is normal or moderately increased. Lumbar puncture reveals an increased spinal fluid pressure. The syndrome has been named "hypertensive encephalopathy" by Oppenheimer and Fishberg and "pseudouremia" by Volhard.

A distinction must be sharply drawn between the above condition and the cerebral disturbances occurring during the course of acute glomerulonephritis, to which the name "uremia" is correctly applied. The use of the latter term should be restricted to those cases with high blood nitrogen values due to renal insufficiency. It is well to recall that extremely high degrees of nitrogen retention frequently occur without producing signs of cerebral irritation. This is illustrated by such conditions as bilateral obstruction of the ureters, corrosive sublimate poisoning and removal of both kidneys. The symptoms in these conditions are progressive weakness, anorexia, nausea, anemia, drow-

underlying cause of the retinal changes. The vascular changes, so prominent in hypertensive vascular disease, may be coincidental in cerebral tumor. Edema of the disk is more marked in intracranial neoplasm and the associated retinal changes are in the immediate neighborhood of the disk. In malignant hypertension the vascular changes and retinal hemorrhages are more pronounced, and papilledema is generally of a moderate degree. Small, flame-shaped hemorrhages may occur in both.

The following case is presented to illustrate the clinical course, the cerebral and retinal manifestations of essential hypertension.

Case Report.—The patient, a white female, aged forty-seven, has been under our observation during the past six years.

Family History.—One sister died of heart disease; a brother has high blood pressure; her mother died of apoplexy at the age of fifty-five.

Medical History.—There have been no past illnesses of any importance, except several attacks of tonsillitis. She had one normal pregnancy at the age of twenty-five. The right breast was removed in 1925 because of carcinoma. In 1926 she began to complain of frequent headaches. At that time a physician told her they were due to high blood pressure.

First Admission (March 18, 1929).—She complained of persistent headache and dimness of vision.

Physical Examination.—The patient was an obese, adult female. The tonsils were infected and several decayed teeth were present. The lungs were resonant throughout and the breath sounds were normal. The area of cardiac dullness was increased (12 cm. to the left of the midsternal line). The heart sounds were normal, except for marked accentuation of the second aortic sound. There was no indication of myocardial insufficiency. Palpation of the peripheral arteries revealed no unusual changes. Blood pressure was 200 systolic and 110 diastolic.

Ophthalmoscopic Examination (March 20, 1929; Dr. S. L. Olsho).—O. D.: The media is clear. The disk is of good color and the edges are sharp. The veins are distended and compressed where they cross the arteries. The smaller arteries are very tortuous, but the caliber is not irregular. There are several small hemorrhages on the temporal side of the disk.

O. S.: The changes are more pronounced in this eye; the arteries are more irregular and tortuous. The disk edges are sharp. There is a large hemorrhagic area on the temporal side of the disk, with streaky prolongations extending toward the macula.

Laboratory Data.—Urine: Occasionally contained a trace of albumin, rarely a few hyaline casts, no sugar, pus or red blood cells.

Blood: Hemoglobin, 82 per cent; erythrocytes, 4,500,000; leukocytes, 6700; the differential count was normal.

Wassermann and Kahn: Negative.

are narrowed is well illustrated by the appearance of the retinal vessels in hypertensive vascular disease. The narrowing of the arterioles causes ischemia of the brain tissue and increased permeability of the capillaries, resulting in the formation of edema; the edema contributes toward the intracranial pressure and anemia. The cerebral irritative phenomena probably result from the combination of these factors.

The associated retinal changes contribute more toward the diagnosis and prognosis than any other single feature. These changes are rarely, if ever, absent in the malignant stage of essential hypertension. Angiospasm, hypertension and increased intracranial pressure are the factors responsible for the damage to the retina. The essential features of the condition are narrowed arteries, distended veins, "cotton-wool" patches, flame-shaped hemorrhages and papilledema. Many observers are of the opinion that these changes have the same ophthalmoscopic appearances and the same pathogenesis as the retinal changes occurring during the latter stage of acute glomerulonephritis; hypertension and vascular spasm being the underlying factors in both. In either case, the prognosis is grave, especially so if toxemia of pregnancy and trench nephritis can be excluded. Patients seldom live longer than two years, rare cases have lived four to six years. Any improvement in the retinal damage is temporary and usually runs parallel with reduction of the hypertension. Edema of the disk and surrounding retina becomes more marked during acute cerebral disturbances; such changes are always associated with a definite increase in the blood pressure and intracranial pressure. The latter may be so great as to result in choked disk. Such cases, with choked disk, headache, vomiting, convulsions and increased spinal fluid pressure, bear a striking resemblance to brain tumor.

It may be difficult or impossible to determine from the appearance of the eyegrounds alone, whether they are the result of essential hypertension, intracranial neoplasm or renal disease. Consideration of a careful history, general physical examination and certain laboratory data usually is necessary to ascertain the

left and the patellar and Achilles reflexes were exaggerated. Tactile and pain senses were not involved. There was no ataxia heel-to-knee test.

Treatment was directed toward reducing the intracranial pressure. Phlebotomy was performed and 400 cc. of blood removed. Four fluidounces of 50 per cent magnesium sulphate solution was given by mouth. The bowel was thoroughly emptied by means of enemas. This apparently did not result in any immediate improvement, so at 9 P. M. (nine hours after admission) a lumbar puncture was performed and fluid was drawn off until the pressure fell from 29 to 19 mm. of mercury. The following morning signs of considerable improvement were noted. The blood pressure was 210 systolic, 110 diastolic. The headache was greatly relieved and the motor function in the left arm was nearly normal. Lumbar puncture was repeated and more fluid withdrawn. Fifty per cent magnesium sulphate solution was administered by rectum twice daily. On the second day, complete use of the left arm had returned and the patient was quite comfortable. Ophthalmoscopical examination on the fourth day (December 13th) showed a reduction in the swelling of the disks to one diopter in the right eye and two diopters in the left. Hemorrhagic areas were more conspicuous. On the fourth day, all neurological signs were normal, the blood pressure was 195 systolic and 110 diastolic. The maximum concentration of the urine was 1.008. There was a marked increase in the volume of the night specimen.

Daily urine examinations revealed essentially the same features as on admission. The blood nonprotein nitrogen fell to 26 mg. per cent. Progress in the patient's symptoms was continuous, although the blood pressure remained above 185 systolic and 110 diastolic. Several small retinal hemorrhages and the tortuous, irregular arteries were present, but the swelling of the disk and adjacent retina had entirely disappeared. The patient was allowed to return to her home on the twenty-fourth day.

Third Admission (February 29, 1932).—She resumed her usual work after leaving the hospital and was comparatively comfortable, except for frequent headaches. A few days before readmission, her headache became more severe and she complained of rapidly failing vision and dizziness. On the day of admission, paralysis of the right arm and leg suddenly developed.

Physical Examination.—The patient was in deep coma, and death occurred three hours after admission.

Laboratory Data.—Blood Examination: Hemoglobin, 76 per cent; erythrocytes, 4,200,000; leukocytes, 16,000 per cu. mm.

Blood Sugar: 128 mg. per 100 cc.

Blood Nonprotein Nitrogen: 48 mg. per 100 cc.

The spinal fluid pressure was greatly increased (32 mm. of mercury) and contained many red blood cells.

Autopsy Diagnosis (Dr. B. L. Crawford).—The examination was limited to the head. Cerebral hemorrhage left occipital lobe with rupture into the left lateral ventricle. Arteriosclerosis of the cerebral vessels.

Discussion.—This case presents several interesting features which are not common during the course of essential or primary

Blood Nonprotein Nitrogen: 27.75 mg. per cent.

Blood Sugar: 86 mg. per cent.

Phenolsulphonephthalein Test: The total two-hour output was 50 per cent.

The two-hour specific gravity fixation test showed a moderately low specific gravity, with an increase in the volume of the night specimen.

Progress.—A diagnosis was made of essential hypertension, neuroretinopathy and early arteriosclerotic kidneys. The patient was placed upon a low salt diet and given complete rest in bed. The infected teeth and tonsils were removed. Her condition gradually improved as indicated by the fall in blood pressure and the relief of the symptoms. The blood pressure dropped to 160 systolic and 100 diastolic. She returned to her home on the twentieth day.

Second Admission (December 10, 1931).—Since leaving the hospital in 1929 she has been able to continue with her usual housework, but during the past six months the headaches have been more frequent and severe. The members of her family noticed she was very drowsy and mentally confused for several days prior to admission. She vomited several times in the past two days.

Physical Examination (1 P. M.).—The patient was mentally confused. Speech was normal but incoherent. The lips and cheeks were a dusky red. The pupils were equal and reacted to light; the eyes could not be rotated to the right. The tongue was protruded in the midline with no tremor. The area of cardiac dullness was considerably enlarged, the left border being 16.5 cm. to the left of the midsternal line. The blood pressure was 260 systolic, 120 diastolic. There was no edema of the ankles. All deep reflexes were exaggerated. Babinski's sign was absent. There was bilateral ankle clonus, more pronounced on the left. There was no motor weakness or paralysis.

Röntgenological Examination (December 20, 1931; Dr. John Farrell).—There was no evidence of carcinomatous metastasis in the skull or chest.

Ophthalmoscopic Examination (December 10, 1931; Dr. E. J. Shannon).—O. D.: The media are clear. The disk is swollen three diopters, the margins are visible but blurred. The vessels are engorged and tortuous; they are seen dipping into the edema of the disk and adjacent retina.

O. S.: The changes are essentially the same as in the right eye. The disk is swollen four diopters and several small flame-shaped hemorrhagic areas are seen at the margin of the edema.

Laboratory Data.—Blood Examination: Hemoglobin, 78 per cent; erythrocytes, 4,400,000; leukocytes, 17,000; the differential count was normal.

Nonprotein Nitrogen: 33.3 mg. per 100 cc.

Blood Sugar: 95 mg. per 100 cc.

Urine Examination: Several specimens showed a trace of albumin, occasional hyaline cast, specific gravity from 1.005 to 1.010, never any red blood cells.

Spinal Fluid Examination: The fluid was under increased pressure (29 mm. of mercury), clear, 5 cells per cm.; sugar, 54 mg. per cent, no red blood cells and the Wassermann was negative.

Subsequent Clinical Course.—The patient's mental condition became progressively worse; cerebration was markedly delayed and perception was slow. There was some twitching of the muscles but no convulsions. Five hours after admission the left arm became paralyzed. Babinski's sign was present on the

imposed upon it by the high blood pressure for a long time, without apparent change in its size.

The renal lesions, in this case, seemed to progress in a parallel course with the general vascular changes. The past history and the absence of signs of glomerulonephritis exclude primary renal disease as a cause of the hypertension. We may interpret the changes in renal functional activity as being due to nephrosclerosis or arteriosclerosis of the kidney. Unfortunately, the autopsy was limited to the head, so these observations could not be confirmed. The kidney damage is well demonstrated by the diminution in the concentrating ability of these organs. During the first admission (1929) the maximum concentration of the urine, as shown by the two-hour specific gravity fixation test, was 1.018; two and one-half years later 1.008 was the greatest degree of concentration. Although the damage to the renal tubules was great, renal compensation was maintained by the excretion of a large volume of urine at a relatively low specific gravity. We may assume that the compensation was sufficient, because the blood nonprotein nitrogen never rose above 33.3 mg. per cent, until the last admission in a preagonal state, it rose to 48 mg. per cent.

The cerebral manifestations of essential hypertension predominated throughout the course of the disease in this case. This is in contrast to other cases in which the renal or cardiac symptoms predominate. Occasionally, however, the disease is not discovered until a grave accident, like cerebral apoplexy or coronary occlusion occurs. The probable course of events responsible for the cerebral symptoms, which occurred during the second admission, was spasm of the cerebral vessels, resulting in ischemia of the brain tissue and edema. The transitory paralysis of the left arm cannot be attributed to hemorrhage or embolism. The presence of high intracranial pressure and edema is confirmed by the greatly increased tension of the spinal fluid and the promptness with which the symptoms were relieved by the withdrawal of fluid and the consequent reduction of the pressure. Spinal drainage, in these cases, is not without danger. Too rapid removal of fluid and reduction of pressure has re-

arterial hypertension. The onset was insidious, it was not discovered until the patient was forced to seek medical advice because of frequent headaches, then the condition was apparently well advanced, as indicated by the high degree of blood pressure. There was nothing in the past medical history to predispose to hypertension or nephritis, except possibly several attacks of tonsillitis.

The family history is very significant and illustrates the striking familial predisposition to primary vascular disease. The mother died of cerebral apoplexy at a comparatively early age, fifty-five; of four children, three are known to have suffered from vascular disease; apoplexy accounts for one, another has hypertension and the third died of heart disease which was preceded by high blood pressure. During the first admission, rest in bed, removal of foci of infection and diet seemed to have a favorable effect on the hypertension and the associated symptoms. The systolic blood pressure was reduced to 160 and diastolic to 100. The symptoms were entirely relieved. During the second admission the results were not so successful. However, at this time the disease was well advanced into the malignant stage. Although, the methods of treatment at our disposal did not have any lasting effect on the hypertension, they aided the body to withstand the effects of the disease for a longer period.

Cardiac failure is a frequent cause of death in essential hypertension. In this case, the patient never complained of symptoms indicative of myocardial insufficiency. However, the effect of the disease on the heart is well demonstrated by the increase in the area of cardiac dulness at each successive period of observation. Such marked enlargement was not due to hypertrophy alone; dilatation was probably present and symptoms of failure were inevitable, if a weaker structure—cerebral artery—had not given way first. There is no doubt that early symptoms of myocardial insufficiency were present, but the cerebral manifestations predominated and were so severe as to completely overshadow all other symptoms. Hypertension is usually accompanied by obvious cardiac enlargement. In rare cases the heart is capable of withstanding the increased work

sulted in sudden death. If the fluid is under great pressure, it should be withdrawn slowly, the pressure being carefully checked by the use of a manometer. It is better to repeat the tap after a few hours than to reduce the pressure to normal at one operation.

The retinal changes, consisting of hemorrhagic areas, tortuous narrow arteries, distention of the veins and moderate edema of the disk, are common findings in the malignant phase of essential hypertension. Cases with swelling of the disk of three or four diopters are not uncommon, and in rare instances it has amounted to six diopters. Choked disk with the cerebral manifestations of essential hypertension present a clinical picture which might readily be confused with that of brain tumor. Subtemporal decompression has been performed in a few cases as a therapeutic measure. In others, it has been done purely on an erroneous diagnosis.

Summary.—A patient is presented to illustrate some of the visceral changes associated with primary arterial hypertension. The cerebral manifestations predominated in this case. Paralysis of one arm, choked disk and paralysis of the external rectus muscle, strongly suggested a localized cerebral lesion. The past history of essential hypertension with retinal changes prevented our making a diagnosis of brain tumor, but the possibility of neoplasm complicating hypertension still existed. The rapid improvement in the systemic, cerebral and eye manifestations, following treatment, excluded the possibility of the increased intracranial pressure being due to brain tumor.

The case further illustrates the similarity of this syndrome to the cerebral manifestation occasionally associated with uremia due to renal insufficiency. The necessity for differentiating these two conditions is obvious, both from a therapeutic and prognostic standpoint.

Let us consider for the moment anemias due broadly to deficiency in production. We find pernicious anemia and chlorosis in the same group. Yet how different they are in their clinical and hematological blood picture and how different is the therapy in each.

Witts has more recently suggested a classification of two broad pathologic groups of anemias based on the activity of the erythron, which seems very sound fundamentally, but has certain objections. The first group consists of a hypoplastic or aplastic bone marrow; the second a hyperplastic. This second group is divided into a hemopoietic or active subdivision and an anhemopoietic or passive group (maturation anemias). With this classification it would be difficult to pigeon-hole an anemia due to chronic hemorrhage, for example. The pathology responsible for the hemorrhage, ulcer, carcinoma, etc., would probably be far removed from the pathology present in the bone marrow (hyperplasia). Minor criticisms of the sort can be raised, but fundamentally it is the most logical classification of the anemias with which I am familiar, for it satisfactorily includes not only the hemopoietic function of the erythron, but also the hemolytic function, which in certain anemias is the most important feature. Unfortunately the same objections I have already raised hold true against this classification. Anemias of the same fundamental pathology give different peripheral blood pictures, and it is on a peripheral blood picture largely that a diagnosis of anemia is made and treatment instituted.

Classifying the anemias on the peripheral blood picture alone might be quite illogical, unless it would aid the physician in diagnosing and treating his patient; then it would be justified, even though etiologically it were entirely unfounded. Physicians primarily are concerned with the successful treatment of disease, therefore any means furthering this aim should at least be tried and if found helpful should be adopted. I believe there are such aids which have gained a new recognition within the past few years and which seem to offer a logical basis for the specific therapy of certain types of anemias. I shall endeavor to present these briefly.

CONTRIBUTION BY DR. J. H. CLARK

FROM THE LABORATORIES OF THE PHILADELPHIA GENERAL
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THE CLINICAL AND THERAPEUTIC VALUE OF COR- PUSCULAR CONSTANTS (BLOOD INDICES) IN THE ANEMIAS

WITHIN the past decade, each year almost has seen some advance in the diagnosis, treatment or better understanding of the cause or causes underlying certain types of anemia, and some years have witnessed the description of hitherto unrecognized entities. These newer contributions have made it necessary for us to revise our conceptions of the old-fashioned primary and secondary anemias, the so-called "large cell anemias" with a color index greater than one, and the chlorotic or secondary type with a color index less than one.

It is now well recognized that many of the so-called "secondary anemias" have an entirely different type of etiologic factor at work, as well as an entirely different peripheral blood and bone marrow picture. A single comparable example will suffice. In infestation with *Diphyllbothrium latum*, there is a high color index with a large cell type of anemia, yet the anemia is secondary to the broad fish tapeworm. In the rarely seen chlorosis, on the other hand, there is a low color index, the cells are smaller than normal, yet the anemia is secondary to a lack of certain materials or a dietary deficiency. The same criticisms can be advanced against the so-called "primary anemias."

Quite recently an etiologic basis for the anemias has been offered, based first on deficiency in production due to lack of material or tissue; second, abnormal destruction, and third, loss of blood. Here again one finds entirely different peripheral blood pictures, due basically to comparable etiologic factors.

ably the patient is suffering from some chronic infection, toxin or possibly a nonbleeding malignancy (see table). If the mean corpuscular hemoglobin concentration or saturation index on the other hand is well below normal then the anemia is most probably due to chronic hemorrhage or dietary deficiency. Treatment would consist primarily in locating the source of hemorrhage, trying to stop it, giving massive doses of iron, the secondary anemia fraction of liver and small doses of copper, singly or in combination. If the anemia is associated with hypochlorhydria give dilute HCl freely and regulate the diet.

Of the corpuscular constants mean corpuscular hemoglobin or color index seems the least valuable. It is practically always low in the hypochromic microcytic varieties of anemia and almost always lower than normal in the simple microcytic variety. Color index, however, has always been the most popular index, because it is the simplest of calculation, being based on the two characteristics of blood usually examined in anemia, *i. e.*, hemoglobin and red blood cells.

Mean corpuscular hemoglobin or color index does serve, however, to classify more accurately certain patients whose corpuscular volume falls into one group and corpuscular hemoglobin concentration into another. For example, a patient is found to have the following blood examination: Red blood cells, 2,650,000; hemoglobin, 5.5 Gm.; volume packed cells 20.5 per cent; corpuscular volume is 77 cu. μ (simple microcytic by Wintrobe's figures). Corpuscular hemoglobin concentration is 27 per cent, distinctly hypochromic. So far then our corpuscular constants are somewhat at variance. Mean corpuscular hemoglobin is 21 $\gamma\gamma$ again hypochromic. Therefore this patient probably has a hypochromic microcytic anemia rather than a simple microcytic, because two constants are for the former. As a matter of fact this patient had a carcinoma of the stomach, a condition easily accounting for the lack of clear-cut blood picture.

To find the particular anemic entity from which the patient is suffering in the general groups of microcytic or normocytic variety one must, of course, have recourse to the other blood ex-

To begin with the first step in the successful treatment of an anemic patient is an accurate diagnosis. After the history is taken and physical examination made, the first step in arriving at the diagnosis has probably been a blood count, consisting usually of a determination of the number of red blood cells and leukocytes per cubic millimeter, the percentage of hemoglobin and a differential count, or else of a red blood cell count and hemoglobin estimation, with possibly the color index calculation. Actually but one other determination besides a red cell count and hemoglobin estimation is necessary in many instances to pigeon-hole an anemic patient into a broad group, which (group) is generally amenable to a fairly specific type of treatment. This one other determination is the volume of packed cells or what was formerly spoken of as an estimation of the red blood cells by an hematocrit determination.

The determination of the volume of packed cells is one of the tests, the value of which has been emphasized by Haden within the past few years, although he gives credit for its usefulness to Capps, who first described its value in 1903. It can be easily made from fingertip blood in office practice, using the Van Allen hematocrit, or by vena puncture in laboratories with more elaborate equipment. We have used both methods at our laboratories with equally good and, what is more important, equally accurate results, in a small series of bloods expressly examined with this in view. The only precautions to be observed have already been emphasized by Wintrobe in particular; first, a knowledge of the anticoagulant used and the amount of shrinkage caused by it, for which allowance must be made in calculating the various indices or corpuscular constants, and second, centrifugation until the volume of packed cells is constant, regardless of time necessary or revolutions per minute of the centrifuge used.

It is necessary to know the error inherent in the counting chamber and pipettes used, either by personal preliminary determinations or by using only those certified by the Bureau of Standards, and also to know the limitations and errors present in the method of hemoglobin estimation used. I would like to

12.9 Gm.; volume packed cells 38 per cent. Indices and constants were as follows:

$$V. I. = 1.02$$

$$C. I. = 1.06$$

$$S. I. = 1.04$$

$$M. C. V. = 89 \text{ cu. } \mu$$

$$M. C. Hb. = 30 \text{ } \gamma\gamma$$

$$M. C. Hb. C. = 34 \text{ per cent.}$$

A total of 2000 cc. of fluid was given within the next twelve hours including 250 cc. by vein, some by hypodermoclysis and some by mouth. The day following she was in good condition, but because of her thirst was given fluids freely by mouth. Thirty-six hours after admission her blood was as follows: Red blood cells, 3,370,000; hemoglobin 10.65 Gm.; volume packed cells 30 per cent. Indices and constants showed practically no change.

$$V. I. = 1.01$$

$$C. I. = 1.10$$

$$S. I. = 1.08$$

$$M. C. V. = 86 \text{ cu. } \mu$$

$$M. C. Hb. = 31 \text{ } \gamma\gamma$$

$$M. C. Hb. C. = 35 \text{ per cent.}$$

It would seem, therefore, that dehydrated states had practically no effect on either blood indices or corpuscular constants.

It is well known that whole liver extract is not specific for all anemias, but only the maturation anemia of the type of Addison-Biermer showing cells larger than normal. It is equally well recognized that iron, copper, etc., give the most spectacular results in those anemias characterized by small cells and low corpuscular hemoglobin concentration. Both of these larger groups are most easily recognized by their peripheral blood pictures and corpuscular constants. Since the diagnosis of the anemias and their appropriate treatment are most readily established by calculation of the corpuscular constants, and since dehydration has no effect on these it would seem logical to classify the anemias on their peripheral blood picture and corpuscular constants since this offers, as well, a logical basis for treatment.

aminations mentioned if these have not already been done, as leukocyte count and differential, as well as reticulocyte count, fragility, icterus index, etc., in certain special cases. But by the calculation of the mean corpuscular volume and corpuscular hemoglobin concentration, based only on three actual blood examinations, many types of anemia have automatically been ruled out and the diagnosis has been narrowed down to relatively few possibilities.

I mentioned previously that the determination of corpuscular constants not only seems preferable but also more accurate. Generally they run fairly parallel with the indices, but occasionally bloods will be encountered in which the blood indices will be at variance with the corpuscular constants and in such cases I have usually found that the corpuscular constants more accurately classify the blood, due largely to the more narrow limits of each constant, as determined by Wintrobe in the different groups. Such a careful separation has not been attempted in the indices, although Osgood and Haskins have tabulated some 200 cases with maximum, minimum and average, but they have not specified the mean limits. A single example will suffice. A patient with carcinoma of the stomach shows the following figures on blood examination: Red blood cells, 4,320,000; hemoglobin 11.3 Gm.; volume packed cells 34.5 per cent. Blood indices are as follows: V.I., 0.94; C.I., 0.90; S.I., 0.98. All within normal limits. The corpuscular constants, however, show the blood to be microcytic: C.V., 79 cu. μ ; C.Hb., 26 $\gamma\gamma$; C.Hb.C. 33 per cent, and as will be seen in the table below, such a patient usually shows a simple microcytic anemia, unless bleeding is prominent.

Although Capps as long ago as 1903 showed that variation in cell size is not due to osmosis, some doubt has been expressed about the effect of dehydration on the blood indices and corpuscular constants. Two examples will serve to show that if there is any influence it is quite negligible.

A few weeks ago a patient entered our diabetic ward with impending coma. She was much dehydrated. Immediate blood examinations showed red blood cells 4,260,000; hemoglobin

all times. During the year 1932 there were 461 discharges from the wards of this department. Eleven patients were nondiabetics. There were 382 individual diabetic patients, the balance of 68 being due to patients who had one or more readmissions. No account is taken of patients in the large diabetic out-patient clinic, who were not admitted into the wards.

Some idea of the material with which we are concerned may be gained from the following tables, giving age distribution, admission blood chemistries, and insulin requirements at discharge.

TABLE 1
AGE DISTRIBUTION OF PATIENTS

Age, years.	No. of patients.	Percentage of total.
1-10.....	3	0.8
11-20.....	18	4.7
21-30.....	16	4.2
31-40.....	27	7.0
41-50.....	87	22.8
51-60.....	110	28.8
61-70.....	86	22.5
70-90.....	35	9.5
	<u>382</u>	

It is to be noted that 60.5 per cent of the patients were over fifty years of age. As to age of onset and duration of the diabetes, so many of the patients were unreliable in their histories as to make tabulations of these data of doubtful value.

Admission blood chemistries of 437 cases are shown in Table 2. Of 450 diabetic cases there were 13 readmitted on which no analyses were made until some hours after treatment was begun.

There is a *decided tendency*, when the blood sugar is markedly elevated, for the CO_2 to be depressed, but this correlation is quite variable. When the blood sugar is above 500 at admission, it is uncommon for the CO_2 to be above 30, and of the cases admitted to our wards during 1932 this happened in only 4. The first 3 of these cases had had no treatment for diabetes, and the fourth had broken her diet and insulin regimen. The first (A. J.) was a woman of sixty-six, admitted with a blood sugar of 520 and a CO_2 of 44. She died five days later of broncho-

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DIABETES MELLITUS. REPORT OF CASES AT PHILADELPHIA GENERAL HOSPITAL DURING 1932

DIABETES mellitus occupies a unique position in that there is no other disease which is so prevalent, which carries such serious consequences, but for which we have such adequate therapeutic measures. Although there are still many serious gaps in our knowledge of carbohydrate metabolism, the case of diabetes which cannot be controlled by the proper use of diet and insulin is rare indeed, if treatment is begun before the onset of serious complications. Although we have some knowledge of the factors which predispose to diabetes, the incidence of the disease continues steadily to increase.^{1, 2} In spite of the very great advances which have been made during the past two decades, the application of the improved therapy has failed to keep pace with the increased incidence, and the mortality rate also has been markedly on the increase.

In any large city hospital one is apt to see diseases and their complications in advanced stages, due to ignorance, neglect and economic circumstances. The material appearing in this paper is a report of cases which were on the wards of the Division of Metabolic Diseases at the Philadelphia General Hospital during the year 1932. The diabetics of the entire hospital are concentrated in this department regardless of other complications or conditions, except those patients suffering with open tuberculosis, contagious diseases, unmanageable psychopathic conditions, and some cases of malignancy. The department has its own laboratories and diet kitchen, and immediate cooperation on the part of the laboratory staff and dietitians is available at

the urea nitrogen was 150. At all times she was mentally clear until a few minutes before her death, which occurred suddenly on May 11th. It is suggested that the extreme grades of the hyperglycemia in such cases is due in part to a diminished ability to excrete sugar.

The insulin requirements of those cases considered standardized at discharge are recorded in Table 3. Eighty-four cases, who died or who left against advice before standardization was completed, are not included.

TABLE 3
DAILY INSULIN REQUIREMENT AT DISCHARGE

Insulin.	No. of patients.	Percentage.
None.....	49	13.4
0-10 U.....	23	6.3
11-20 U.....	39	10.7
21-30 U.....	59	16.1
31-40 U.....	50	13.7
41-60 U.....	116	31.7
Over 60 U.....	30	8.2
	<u>366</u>	

It is apparent that our patients take more insulin than is reported by many other clinics. We feel that this is not accounted for by our dietary prescriptions. We usually prescribe 100 to 120 Gm. of carbohydrate, rarely more, and not often less. The requirements of adults are usually calculated to be 30 calories per kilogram of standard weight. The total calories are pushed above this figure only in case of marked undernourishment and failure to gain weight. Many overnourished patients received only 20 calories per kilogram of standard weight or even less.

In explanation of these insulin figures two points are worth noting. The first is that the figures as given are those occurring at the time each patient is discharged from the hospital. During the course of subsequent treatment, with the patient in balance, a considerable amount of tolerance is often recovered and the insulin requirement consequently becomes less. The second point is that due to reduced insulin budgets in other hospitals, the diabetics requiring large amounts of insulin have tended to gravitate to the city hospital.

TABLE 2

ADMISSION BLOOD CHEMISTRIES ON 437 CASES

Admission blood sugars.				No. of cases.
Below 60	mg.	per 100 cc.		4
60-115	"	"	"	34
116-200	"	"	"	106
201-300	"	"	"	154
301-400	"	"	"	85
Over 400	"	"	"	54
Admission CO ₂ .				No. of cases.
Above 70	cc.	per 100 cc.		2
50-70	"	"	"	276
40-49	"	"	"	91
30-39	"	"	"	20
20-29	"	"	"	17
Below 20	"	"	"	31
Admission blood urea nitrogen.				No. of cases.
Below 16	mg.			308
16-25	"			81
Above 25	"			48

pneumonia and uremia, the urea nitrogen having been 40 at admission, and 93 at death. The second case (C. D.) was a woman aged sixty-two, admitted with a blood sugar of 588 and a CO₂ of 40. She died nine hours after admission with a urea nitrogen of 145. Postmortem examination showed bronchopneumonia and extreme toxic nephrosis. The third case (G. H.) was a man of sixty-six with an admission blood sugar of 502, CO₂ of 39, and urea nitrogen of 34. The fourth case (M. F.) was a woman of forty-nine, whose blood sugar was 576, CO₂ 52, and urea nitrogen 12. The last two recovered. It is noteworthy that the first 3 cases all showed kidney damage.

A most marked disproportion in the blood chemistry occurred in a case recently admitted (A. R.), a woman, aged sixty-five, who had been attending our out-patient clinic for five years and for the most part had been well controlled with 30 units of insulin. A few days before her admission on May 3, 1933, she had what her family physician considered an attack of grippe. At admission the blood sugar was 916, CO₂ 34 and urea nitrogen 115. She was given 120 units of insulin and thirteen hours after admission the blood sugar was 290 and CO₂ 48. On May 9th

milder cases of acidosis were included, our mortality rate might be made to appear quite favorable. Our reason for selecting the CO_2 figure of 29 as the basis for this table is partly because we have seen no patient die with an admission CO_2 higher than this who did not have other lesions which we considered more potent as a cause of death than the acidosis, and partly in order to have a definite criterion. We are well aware that the degree of clinical acidosis runs parallel with the degree of chemical acidosis only very roughly. We all have seen cases who were wide awake with a CO_2 of 10 or less, and other cases who were completely knocked out when the CO_2 was much higher. The degree of dehydration, the loss of base, the condition of the kidney and heart functions are often quite as important as the actual level of acidosis. Perhaps there are also individual variations of susceptibility to the poisons of acidosis, just as individuals vary widely in their susceptibility to the same dose of alcohol and other poisons.

In Table 2 it will be noted that there were 111 cases with the admission CO_2 lying between 30 and 49. Doubtless not a few of these cases were suffering from acidosis clinically more severely than some of the cases which have been listed in Table 5.

Of the 48 cases in Table 5, 25 had complications and 23 were uncomplicated. Of the 25 cases 12 died, 10 of whom had complications possibly of sufficient severity to have caused death without the acidosis. Of the 23 cases without complications 5 died.

It is of interest to note that of the 11 cases in Table 5 in which the urea nitrogen was above 25, 8 died and only 3 recovered.

The chief purpose of this paper is to give a picture of diabetes as seen in a large city hospital and to call attention again to the fact that diabetes and its complications are causing a large number of deaths, many of which are unnecessary. We feel that possibly a third of our deaths could have been avoided if we had received the cases earlier. This certainly applies to all the uncomplicated coma deaths, to perhaps half of the coma deaths

Seventy-four patients died on the wards. As might be expected the four agents of destruction were acidosis, arteriosclerosis, gangrene and infection. As these frequently do not attack singly, in compiling a table of mortality statistics it is often very difficult to decide to which group a given case should be assigned.

TABLE 4
CAUSES OF DEATH

Acidosis present.....	17	Tuberculosis.....	1
Heart disease.....	14	Miscellaneous.....	5
Gangrene and infections of the feet	13	Mesenteric thrombosis	
Infections.....	12	Cirrhosis	
Cerebral accidents.....	6	Hypoglycemia	
Kidney disease.....	3	Fractured femur	
Cancer.....	3	Hemorrhage from peptic ulcer	

That there was only one death due to tuberculosis is due to the fact that most patients having both diabetes and tuberculosis are treated on the tuberculosis wards.

The case of hypoglycemia occurred in a man of thirty who had been in coma a number of times as a result of breaking his diet-insulin regimen while on alcoholic debauches. Upon this occasion he returned home after a spree lasting several days, took his evening insulin dose of 20 units and then vomited his supper. Later he became drowsy, and the family assuming that he was going into coma gave him 30 units. Later, as he did not improve, they administered another 30 units, and then all went to sleep. In the morning he was found profoundly unconscious, and brought to the hospital. His admission blood sugar was 22. Intravenous glucose did not revive him and he died four hours after admission.

In the group "acidosis present" are included all cases who had a CO_2 of 29 or less at admission, regardless of whether any complication was present sufficient to cause death. In compiling mortality statistics of acidosis, the rate will be influenced not only by the severity of the cases and the adequacy or inadequacy of their treatment, but by the criteria employed in gathering the statistics. If those cases which had other pathology sufficient to cause death were excluded, and if many of the

complications and dangers, and its modern treatment, in the elimination of much poor treatment and in the suppression of a vast amount of downright quackery in connection with the use of nostrums supposed to be beneficial to diabetes.

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TABLE 5
PATIENTS ADMITTED WITH CO₂ OF 29 OR LESS

	Age.	Sex.	Adm. B. S.	Adm. CO ₂ .	Adm. Urea N.	Time out of acidosis.	Time died.	Complications.	Re- sult.
1. B. A.	16	F.	728	14	18	..	9 H.	..	D.
2. G. A.	54	M.	372	26	14	6 H.	48 H.	Abscess chest wall Staph. aureus septicemia.	D.
3. T. B.	21	F.	464	14	18	12 H.	R.
4. J. B.	19	M.	320	28	9	7 H.	..	Abscess neck.	R.
5. A. B.	55	F.	400	10	28	..	18 H.	Erysipelas.	D.
6. M. B.	41	F.	632	12	24	9 H.	..	Hyperthyroidism.	R.
7. M. B.	600	11	27	7 H.	..	Hyperthyroidism.	R.
8. M. B.	640	16	55	..	22 H.	Hyperthyroidism.	D.
9. L. C.	49	F.	532	17	16	..	13 H.	Advanced pulmonary tuber- culosis.	D.
10. R. D.	45	F.	480	26	90	8 H.	8 days	Chronic and subacute neph- ritis.	D.
11. A. E.	20	F.	462	16	20	23 H.	R.
12. C. F.	17	M.	280	16	12	12 H.	..	Acute pharyngitis.	R.
13. A. F.	35	F.	752	19	60	..	6 H.	..	D.
14. J. G.	16	M.	574	17	14	11 H.	..	Bronchopneumonia.	R.
15. J. G.	280	20	18	8 H.	R.
16. J. G.	400	21	22	6 H.	R.
17. L. H.	65	F.	960	15	75	..	11 H.	..	D.
18. A. J.	39	M.	662	12	22	7 H.	..	Erysipelas.	R.
19. G. J.	47	F.	900	23	48	8 H.	26 H.	Lobar pneumonia.	D.
20. E. K.	17	F.	288	17	7	31 H.	..	Acute follicular tonsillitis.	R.
21. E. K.	330	18	11	22 H.	R.
22. A. K.	25	M.	290	13	12	9 H.	R.
23. T. K.	39	M.	500	27	53	..	12 H.	Bronchopneumonia.	D.
24. E. K.	40	F.	768	14	15	8 H.	R.
25. H. L.	28	M.	388	17	12	9 H.	R.
26. J. L.	55	M.	480	11	21	..	7 H.	Extensive gangrene of foot.	D.
27. J. M.	4	M.	440	14	7 H.	Pertussis.	D.
28. C. M.	24	F.	340	24	14	4 H.	R.
29. F. M.	35	F.	338	20	14	7 H.	..	Ischiorectal abscess.	R.
30. M. N.	33	F.	540	15	30	10 H.	..	Bilateral suppurative paro- titis.	R.
31. N. O.	10	F.	280	12	10	13 H.	R.
32. C. P.	72	M.	328	29	15	3 H.	..	Gangrene of foot, mid thigh amputation 4 hours after adm.	R.
33. S. R.	15	F.	320	27	11	6 H.	R.
34. M. S.	42	F.	400	27	24	3 H.	..	Inflammatory arthritis.	R.
35. H. S.	57	M.	414	27	26	6 H.	14 H.	Massive carbuncle of neck.	D.
36. A. S.	15	F.	424	12	10	..	11 H.	..	D.
37. J. S.	12	M.	304	20	18	12 H.	R.
38. W. S.	18	M.	416	18	17	10 H.	..	Lobar pneumonia.	R.
39. W. S.	23	M.	364	22	11	8 H.	R.
40. C. S.	37	F.	460	15	16	..	12 H.	Abscess bartholin gland.	D.
41. I. S.	22	F.	450	18	22	..	12 H.	..	D.
42. M. S.	9	F.	480	18	14	14 H.	R.
43. M. S.	324	22	12	4 H.	R.
44. J. T.	13	M.	344	17	10	7 H.	R.
45. H. W.	17	F.	448	9	12	9 H.	..	Suppurative mastoiditis.	R.
46. R. W.	30	M.	720	24	65	11 H.	R.
47. S. W.	62	F.	300	9	11 H.	Undetermined infection.	D.
48. M. Z.	26	F.	608	14	17	10 H.	R.

with complications, to most of the gangrene deaths and to many of the infection deaths. In spite of possessing excellent facilities for treating diabetes, we are not at all sure that we shall be able to reduce our mortality rate materially so long as we continue to receive the present type of cases. The hope for the future lies in the wider diffusion of information about diabetes, its

advanced by Kreysig in 1817 and later supported by Rokitsky. Laënnec, it is reported,³⁶ never applied his invention, the stethoscope, to the chest of a patient with congenital heart disease and Rolleston tells us that Laënnec erroneously assumed that "useful diagnostic signs would not thus be provided."

Hope,²⁴ in 1834, advanced the claim that the most frequent cause of congenital heart disease was a developmental defect. Bouillaud,⁸ in 1835, recognized both this cause and fetal endocarditis as operative. Rokitsky³⁵ spent many years of his busy life in a detailed study of congenital heart disease and in 1875 published his epoch-making monograph. In it he not only described anomalies he had seen but with astonishing accuracy and the wisdom of a great embryologist worked out certain combinations of possibilities from errors in development and predicted their future occurrence. Many of these have since been observed and described in the literature.

Wilkinson King first diagnosed patency of the ductus arteriosus during life in 1847 and a fuller description followed in 1849 from the pen of Bernutz.⁶ A description of the physical signs was given by Gerhardt in 1867.

The advancement of the knowledge of the morbid anatomy of congenital heart disease came chiefly through the work of Louis, Bouillaud,⁸ Peacock (1858),³¹ Rokitsky (1875),³⁵ and Abbott (1908).¹ Roger³⁴ in 1879 described partial defect in the interventricular septum with freedom from cyanosis (*maladie de Roger*).

Etiology.—There are many opinions advanced as to the etiology of these defects. Earlier writers pointed out the resemblance of many to the normal hearts of animals and were content with the explanation of reversion to the primitive. For example, faulty development at any of the stages in the development of the human heart particularly in regard to the septa may produce a two-chambered heart as we see in fish or a three-chambered heart similar to that met with in the frog. Why the faulty development should occur has been explained in various ways. Some believe that there are pathologic currents in the blood stream in the fetal heart which prevent the septa growing

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CONGENITAL HEART DISEASE INCLUDING REPORT OF A CASE OF CONGENITAL HEART BLOCK WITH AU- TOPSY FINDINGS

THIS morning we will spend the hour discussing some of the aspects of congenital heart disease. No doubt, your pathologic studies have led you to believe that this is a very complicated as well as a very rare phase of the subject and consequently relatively unimportant. Perhaps I will agree with you that it is complicated, if we undertake to study in detail all the different anomalies on record and the minute details of all their structural aberrations. No one can deny that it is rare, for these congenital defects comprise less than $\frac{1}{2}$ of 1 per cent of all the heart cases registered in our clinic. Among our children congenital cardiac lesions make up less than 5 per cent of the cases of heart disease. However, I will not agree with you that the subject is relatively unimportant. Perhaps over half of the congenital cardiac defects are *clinically* unimportant but the remainder are apt to become the site of serious infection at any time of the patient's life and this possibility should serve to sharpen our clinical vision and keep us ever on the alert for this condition in cardiac diagnosis.

Historical.—In looking back over the history of our knowledge of congenital cardiac defects it is interesting to note that the first case on record was described by Senac⁴³ in 1749. It consisted of a patient with complete absence of the interventricular septum and this observer explained the cyanosis by the admixture of the venous and the arterial blood. A further survey of the earlier workers in this field shows us that the great Morgagni first reported congenital pulmonary stenosis in 1761. Fetal endocarditis as the cause of congenital cardiac defects was

Symptoms.—There may be no symptoms. On the other hand, if the lesion is marked, symptoms may be severe and incapacitating. As in the acquired form so in the congenital as well, dyspnea is the commonest symptom and it may be present in all degrees. The polycythemia, when present, may give rise to epistaxis and to sluggish and pulmonary circulation. The former may give rise to hemoptysis and the latter to symptoms of central nervous system origin including headache, vertigo, convulsions, transient or persistent paralyses due in some cases to the polycythemia predisposing to cerebral thrombosis. I have been interested in the possibility of coronary thrombosis in this younger group, based on similar etiologic grounds. We must always think of it and search for it clinically and at post-mortem.

Signs.—Some cases will show no signs whatever outside the heart itself. Indeed, in some, you will find no signs over the heart itself and the defect will be revealed to unsuspecting eyes for the first time at autopsy. Of the general signs the first one that comes to your mind, of course, is cyanosis. We could well afford to spend the rest of the hour discussing this sign alone but since time does not permit I will refer you to that excellent monograph by Lundsgaarde and Van Slyke.²⁸ Suffice it to say that the factors concerned are the admixture of the arterial and venous blood through the congenital defect, the lack of sufficient oxygenation of blood in the lungs and the engorgement of the peripheral capillaries of skin and mucous membranes with consequent slowing of the blood stream. Malnutrition is common in these children and again, I repeat, remember the possibility of errors in development occurring outside the heart. Clubbing of the fingers and toes is a prominent symptom but it is not seen in the young infants. It develops after the cyanosis and is closely associated with deficient oxygenation.

Clinical Types.—Of all the possible congenital malformations there are four types which constitute the bulk of the cases which will come to your notice clinically. In our discussion this morning we will stay within clinical bounds and limit ourselves

across and closing off the chambers in a normal fashion. Others claim disease of the fetal envelopes and include syphilis and tuberculosis. The factor of heredity must be given some credence inasmuch as, contrary to previous claims, many of these cases live long enough to raise the question of possible transmission of the tendency. Influences on the mother during pregnancy like fright, operations, etc., have been favored by many as the cause explaining the maldevelopments. These factors during pregnancy are the most favored and popular explanations among the laity for all congenital defects. Difficult delivery will, of course, not account for any except the later lesions. One of the oldest theories, as has been mentioned, is the presence of fetal disease in the fully developed heart. This rôle of fetal disease I believe is a minor one. We must remember, however, in this connection that there are some cases of rheumatic endocarditis directly transmitted from mother to offspring.

Associated Defects.—Congenital cardiac defects are commonly associated with imperfect development in other parts of the body. Mental deficiency is not uncommon in the group and the occurrence of any form more especially the Mongolian type of idiocy should lead us to examine the heart with care. These patients are more apt to show a combination of defects, both inside and outside the heart, and this is certainly a point to keep in mind in diagnosis. The disease factor acting at more than one site in the embryonal development may account for other defects outside the heart. The combination of defects inside the heart structure is possibly caused by pressure effects and may be better understood by a study of the intracardiac pressure changes during development *in utero*. For example, we can see that the pressure effects from a single lesion like congenital pulmonary stenosis tend to keep patent the ductus arteriosus. In other words as White⁴⁷ has stated "instead of our being surprised that congenital cardiac defects are frequently combined we should be more surprised when they are isolated except in certain instances as in the case of pericardial defects, of primary congenital hypertrophy and of coarctation of the aorta."

tion in the electrocardiogram. Despite the greatly increased demands on the right ventricle failure with congestion is rare. During the past year we had the privilege of observing, through the courtesy of Dr. Cogill, a patient with an advanced congenital lesion of this type go through an uncomplicated pregnancy.

Coarctation of the Aorta.—This occurs just before or just at the time of birth and is due to a too-powerful contraction of the fibrous tissue at the site of the emptying of the ductus arteriosus. It usually occurs distal to the subclavian artery and the back pressure effects coincident to the lesion dilate this artery and its branches—more especially the scapular and internal mammary arteries. The blood finds its way through these arteries and their anastomotic links into the lower aorta. So the first sign we may see which would lead us to suspect the lesion in the aorta is the dilatation and pulsation of one of these far distant branches. Other effects of the back pressure may be reflected in the blood pressure readings which are increased in the arms. We may also observe the extreme pulsation in the carotid arteries. The aorta may be shown to be dilated by percussion or fluoroscopical examination. The femoral pulse should always be examined when we suspect the presence of this lesion and should be a routine procedure in all patients with elevations of the blood pressure in the arms. In cases of coarctation of the aorta we will find the femoral pulse absent or feeble and occurring after the pulse at the wrist. Patients we have seen with this lesion have few if any complaints. They seem to bear up well even when following the most strenuous occupations.

Defective Interventricular Septum.—This is the commonest cause of cyanosis occurring in congenital heart disease and forms part of the lesion in the heart I am going to show you this morning. The defect may occur alone and is usually in the upper third of the septum or the membranous part. The blood passes from the left to the right side of the heart through the defect and usually gives a loud long systolic murmur heard all over the precordium but with point of maximal intensity at the fourth left interspace near the sternum. This murmur may be accompanied by a thrill. Sir Thomas Lewis tells us²⁷ that some

to the consideration of the chief findings in these commoner lesions.

Persistent Ductus Arteriosus.—As you recall, in the fetus, this structure carries blood from the pulmonary artery to the aorta. At birth when aortic pressure rises and pulmonary pressure falls this by-path normally shrivels and closes. In some cases where failure of closure occurs due to abnormal pressures in the cavities of the heart continued blood flow through this structure takes place—and the current is from the aorta to the pulmonary artery. We would expect from this description to find the pulmonary artery larger since it is the recipient of this abnormal blood current and this can many times be demonstrated by percussion. Fluoroscopical examination is also of value and reveals both the dilatation and at times an abnormal transmitted pulsation in the pulmonary artery shadow on the left heart border. Listening over the second and third interspaces to the left we hear the characteristic harsh, loud, continuous, machinery murmur and this may or may not be accompanied by a thrill in the pulmonic area. Accompanying this lesion (perhaps as its causal agent) we may find pulmonary stenosis.

Pulmonary Stenosis.—This is a very common congenital lesion and is caused by lack of full expansion of the infundibulum. It may occur from slight to severe grades. In the latter instances there is extreme narrowing of the pulmonary orifice with fusion of the valve cusps. The greater the narrowing the more likely is the lesion to be associated with an opening in the interventricular septum. The current of dammed back blood establishes a path across to the opposite ventricle and this current keeps the septum from completely closing. The lesion gives a systolic murmur to the left of the sternum with maximum intensity at the second or third interspace. Some pulmonary regurgitation may manifest itself in a diastolic murmur in the same locality. These findings are accompanied by a thrill in the second or third interspaces to the left. There is considerable hypertrophy of the right ventricle when the stenosis is of high degree, registering extreme right axis devia-

minute. The liver and spleen were not palpable and the rest of the examination irrelevant.

The child was taken to the heart station of the hospital and electrodes applied and tracings taken at intervals for the next few hours.

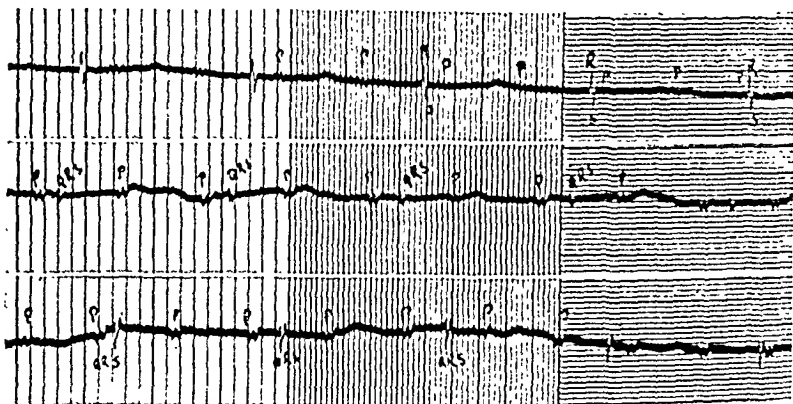


Fig. 155.—Showing complete heart block. The ventricular rate 50; auricular rate 1000.

The first tracing (Fig. 155) shows complete heart block with a ventricular rate of 50. Low voltage and left axis deviation.

At 12.10 p. m. oxygen was administered with a slight improvement in the cyanosis. The tracing was unaffected, the rate remaining at 50 and the complete

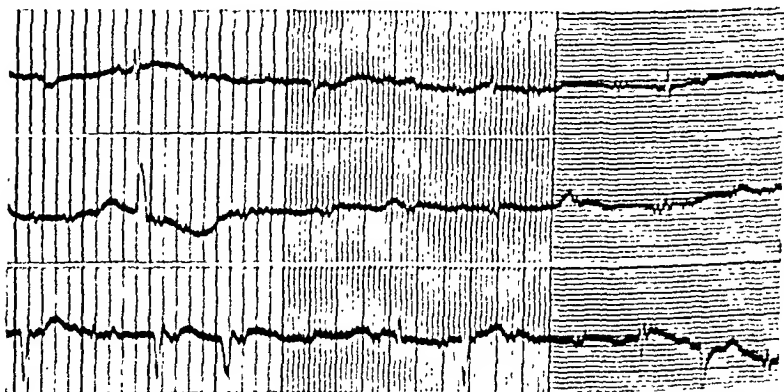


Fig. 156.—Showing occurrence of premature ventricular beats in lead III following atropine in child with congenital heart block.

block persisting. Throughout the following experiments the child was connected to the electrocardiograph and tracings were made at ten-minute intervals.

At 12.15 1/1000 grain of atropine sulphate was given hypodermically

of these cases live on into their forties, even with cyanosis. Of course the chief danger is an implantation of an endocarditis at the site of the lesion.

Defects in the interventricular septum commonly complicate other lesions. We might mention in passing that the most frequent combination of lesions is the tetralogy of Fallot consisting of pulmonary stenosis, interventricular septum defect, dextroposition of the aorta and hypertrophy of the right ventricle. This combination was first described by Peacock³¹ in 1858 but more completely by Fallot¹⁵ in 1888 and is now an established clinical entity bearing the name of the latter. A much rarer but somewhat similar combination of lesions consisting of dextroposition of the aorta, interventricular septal defect, large right ventricle and increased size of pulmonary valve, infundibulum and pulmonary valve and artery is the so-called tetralogy of Eisenmenger¹² (1897).

REPORT OF CASE

M. G., male, aged eighteen hours. The sixth child born to a woman aged twenty-eight. Previous children living and well. No defects noted in either parent. The mother's prenatal period was entirely uneventful. There was no rheumatism in any form and her convalescence was complete. The Wassermann reaction was negative. The delivery was entirely normal and took place at 5 A. M. on May 6, 1932. On delivery the child cried feebly and became extremely cyanotic. The respirations were very shallow and irregular and the child was admitted to the Hospital of the Woman's Medical College of Pennsylvania three hours later.

Examination on admission showed well-nourished, well-developed, white male infant—apparently a full-term baby. No defects noted. Length of body 51 cm., upper extremities 19 cm.; lower extremities 19.5 cm.; weight 8 pounds. Marked cyanosis of body generally and of lips, ears and nails especially is present.

Examination of lungs showed impaired resonance at the left apex posteriorly. Breath sounds harsh over both sides with many crepitant râles throughout. Substernal retraction was present.

Examination of heart: No thrills palpable. The left cardiac border measured 7 cm. from the midsternal line in the fourth interspace. The right border measured 2.5 cm. from the midsternal line in the third interspace. The first sound of the heart obscured by a blowing systolic murmur and the second weak. Another sound follows closely after the second of same weak tapping quality. The systolic murmur is heard all over the chest but the center of intensity is over the second interspace to the left of the sternum. Rate of heart 40 per

The lower border measures 6 cm., the upper border 3 cm., the right border 4 cm. The left border, which is the interventricular groove, is 5 cm. long. The posterior surface is triangular. The point of the triangle is at the right extremity. From the lower border of the interventricular groove is 5 cm. From the upper border of the interventricular groove to the point (right extremity) is 3.8 cm. The left ventricle is more nearly round and measures posteriorly 3 cm. from the interventricular groove to the outer border.



Fig. 158.—x-Ray photograph taken four hours before death. It shows enlargement of heart in all diameters.

The auricles have a peculiar shape. The left auricle is a long thin chamber with a long auricular appendix which curls around the roots of the great vessels so that the tip comes to lie on the anterior aspect of the root of the aorta and touches the upper border of the right auricle in front. The right auricle is larger than the left. It contains a short, curly appendix. On cutting open the ventricles they are found to be of approximately equal size. The *interventricular septum* is intact for the lower two thirds but stops in the region of the undefended space (Fig. 157). The tricuspid and mitral valves are both

There was no further improvement in the color but the heart rate increased to 60 per minute in the tracing. The auricular rate was 100. Complete block persisted.

At 12.30 P. M. another similar dose of atropine sulphate was given (1/1000 grain). At 12.30 many premature ventricular beats began to appear (Fig. 156) and the color improved considerably. Complete block persisted, the ventricular rate falling back to 50 and the auricular to 100 after the cessation of the premature contractions.

The child was taken back to the ward and kept in an oxygen tent until his death at 8 P. M. the same evening. Autopsy the following morning.

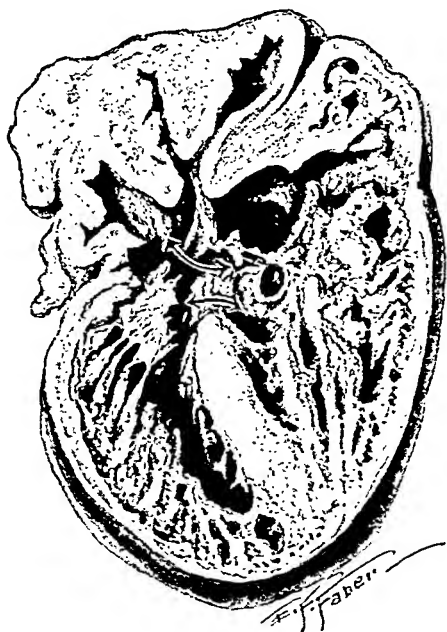


Fig. 157.—Showing defects in interauricular and interventricular septa.

Autopsy Findings.—Thymus, trachea, larynx and bronchi normal.

The Heart.—Pericardium extremely dilated, compressing both lungs, especially the left which lies far back in the thorax. The pericardium is 8 cm. in diameter and contains a small amount of clear fluid. The apex of the heart is opposite the seventh rib. The heart lies so that the right auricular appendage is on the diaphragm on the right side and the apex rests on the diaphragm toward the left. The right ventricle occupies the larger part of the anterior surface and lies transversely on the diaphragm. Six centimeters of the lower border of the heart is occupied by the right ventricle, 1.4 cm. by the left ventricle and about 0.6 cm. by the right auricle. The ventricles, especially the right, have a curious shape. The anterior surface of the right ventricle is roughly quadrilateral.

2. Congenital defect.
3. Neoplasm.
4. Trauma.

In regard to heart block caused by acute infections we first of all think of diphtheria. Smith⁴⁴ has shown that 4 per cent of all cases develop heart block. D'Espine¹³ describes a case of complete heart block in a boy of eight and one-half years with a positive Wassermann reaction and attributes the condition to syphilis. Of the 21 cases of heart block in children collected and tabulated by Eyster and Middleton¹⁴ 10 or approximately 48 per cent are included in this group.

The explanation of the heart block in many of the cases in the second group has not been definitely determined. I assume, of course, that in the case of the patient I have just reported that the septal defect has involved the conduction fibers of the bundle. However, the work of Keith, Monckeberg and Morrison and Flack and Mall does not confirm this view. In most of the cases of septal defect they examined there was surprisingly little change noted in the distribution of the bundle. In the only case on record of complete investigation by serial section and reconstruction by R. T. Grant²⁰ the bundle was seen to be present in a case of cor triloculare passing down in a muscular prominence at the back of the common ventricle, the ingrowth of fibrous tissue resulting in only partial (2:1) heart block during life. We will, of course, proceed at once to harden this specimen and cut serial sections to show the presence of any special conduction tissue and will report the result at a later date. In this second group (heart block due to congenital defects) we have 9 cases in the series collected by Eyster and Middleton or 43 per cent.

Neoplasms of the heart are extremely rare. I include this heading in the proposed classification on account of the case reported by Armstrong and Monckeberg⁴ of a child of five who had pulse of 28 with recurrent attacks of Stokes-Adams syndrome. Death resulted in one of the attacks and autopsy revealed a tumor of the A-V node which was considered to be a primary growth in this location.

present and have the normal number of cusps. The septal cusp of the tricuspid is attached above to a papillary muscle in the right ventricle. The effect of this valve seems to be to direct the main current of blood from the left auricle to the right ventricle. There is no septum above the valves, so that at this point all four chambers meet. The right auricle opens into this space in such a way that the current must have been directed into the left ventricle. The only division between the auricles is a crescentic fold beginning mesial to the superior vena cava and continuing upward and forward until it ends in a band of muscle from which the anterior cusp of the tricuspid valve arises. The pulmonary artery is normal; the aorta has three cusps but is dilated above the cusps.

Vessels are normal. The blood is dark and fluid.

Abdomen and Peritoneum.—The abdomen contains a small amount of blood-stained fluid.

Liver.—Measures $12 \times 7 \times 3$ cm., is large and intensely congested. The lower surface bulges. The cut surface is intensely congested and appears a little cloudy.

Spleen.—The spleen is rather large and firm. An accessory spleen is present.

Pancreas.—Congested.

Kidney.—The right kidney measures 7 cm. with the suprarenal. The right kidney measures 4.5 cm. in length. The left kidney measures 6 cm. with the suprarenal, and 4.5 cm. alone. Both kidneys are intensely congested; otherwise normal. Suprarenals normal.

Urinary Tract.—Normal.

Alimentary Canal.—Esophagus congested. Stomach distended containing mucus and food. Mucosa congested. Duodenum intensely congested. Intestines likewise congested. Here and there are areas of hemorrhage into the intestinal mucosa. Further along the tract are patches of intense congestion with petechial hemorrhages. The lower end of the intestine is distended and contains meconium.

NOTE: Appreciation is hereby expressed to Drs. Bacon, Cogill, Ingleby and Lane for the privilege of reporting this case.

DISCUSSION

Congenital heart block has been reported in association with congenital morbus cordis not more than twenty times in the literature. Heart block, taken as a whole, is likewise infrequent in children. The following etiologic classification is proposed for the cases already described in the literature.

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(a) Diphtheria.

(b) Rheumatism.

(c) Whooping cough, bronchitis, etc.

(d) Syphilis.

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Trauma must be considered as a cause of heart block in childhood. This cause is convincingly set forth in a case reported by Rosenson³⁹ of a boy of ten who, following a blow on the chest while at play, developed weakness and fluttering of the heart followed by a spell of unconsciousness and slow pulse. Electrocardiographic examination revealed heart block which cleared up with rest in bed. The hypothesis is advanced of a slight hemorrhage in or about the node of Tawara or bundle or some similar change in the conduction system.

In conclusion I would like to state that the cardiac irregularities, with the exception of sinus arrhythmia, are rare in childhood. Of the arrhythmias we do meet the rarest is heart block. These disturbances of rhythm and conduction have, until recent years, played a very minor rôle in the diagnosis of congenital heart lesions. However, the more general application of the method of electrocardiography in recent years reveals in some cases changes that are essentially important in diagnosis. In the case before you this morning two arrhythmias were displayed—heart block and premature ventricular contractions. In these congenital heart cases negative electrocardiograms are useful in ruling out the possibility of complicating right-sided lesions like congenital pulmonary stenosis when we have the clinical signs of interventricular septal defect, patent ductus or coarctation. Congenital pulmonary stenosis with a large right ventricle will give us a marked, rather characteristic, right axis deviation. In dextrocardia we see all the waves in lead I inverted and leads II and III reversed.

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In July, 1931, the patient at the age of twenty-six was delivered for the seventh time in another hospital. *x*-Ray studies then revealed an area of increased density in the left chest which had the appearance of an aneurysm of the descending aorta. The patient was discharged in August, 1931, and told to report to the out-patient department. Extreme weakness and aggravated pain when she attempted to get out of bed prevented her from complying with this advice. During September, 1931, the back pain was unusually severe and was associated with a "choking" sensation in the epigastrium which became a sharp pain after drinking cold water. At this time there also developed "neuritis" of the left arm. For these symptoms her doctor prescribed pills which gave her relief but made her very "dopy." She had lost weight, her weight being 79 pounds, while her usual weight was 112 pounds.

Six of her children were living and well; the second child died at the age of two from "intestinal obstruction." Her only illnesses before the age of seventeen were measles, chickenpox, whooping cough, and frequent attacks of sore throat. Serological tests on the blood and spinal fluid at both hospitals were found to be entirely negative.

The patient was first admitted to the Philadelphia General Hospital on November 9, 1931, when the above history was obtained.

Physical examination showed an intelligent, colored female, twenty-seven years of age, very thin and of poor muscular development. The eyes revealed slight exophthalmos, some lagging of the upper eyelids, and round, equal pupils which reacted promptly to light and accommodation. The thyroid was easily palpable. The heart was of normal size, the apex beat was diffuse and there was a marked precordial heave. The rhythm was normal and a soft systolic murmur could be heard at the base and apex. The blood pressure was 120 systolic and 70 diastolic in the right arm, and 160 systolic and 75 diastolic in the left arm. The lungs were clear except for impairment of percussion 3 to 4 cm. to the left of the fourth to the seventh thoracic vertebrae. The abdomen presented no abnormal physical findings aside from marked pulsation of the abdominal aorta and diastasis recti. The extremities showed only exaggerated reflexes.

Laboratory Observations.—The red blood cells were 4,220,000; hemoglobin, 90 per cent; white blood cells, 7700, of which 69 per cent were polymorphonuclear neutrophils. The blood sugar was 76, and the blood urea nitrogen 10 mg. per 100 cc. of blood. The sputum was negative for tubercle bacilli on several occasions. The urine was negative; the blood and spinal fluid Wassermann and gold colloidal reactions were normal. The basal metabolic rate was plus 22. *x*-Ray of the chest showed dilatation of the ascending and descending aorta and deflection of the aortic arch to the left and upward. The *x*-ray diagnosis was aortitis. A flat plate of the abdomen failed to reveal any definite evidence of abdominal aneurysm.

Course.—With bed rest, forced feeding and 30 minims of Lugol's solution daily the patient improved. Her weight rose from 79 to 101 pounds. The basal metabolic rate dropped from plus 22 on November 14th, to plus 6 on November 21st. *x*-Ray of the chest at this time showed that the aortic dilatation was less than on admission.

In August, 1932, the patient was admitted to the maternity department

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NONSYPHILITIC ANEURYSM OF THE LOWER THORACIC AND ABDOMINAL AORTA

THIS clinic I shall devote to the discussion of an unusual case of aortic aneurysm. As the case unfolds you will realize that the patient was not only a problem in diagnosis antemortem but is still a problem in etiology postmortem.

Aneurysm of the aorta so often results from syphilis that some able observers have come to the conclusion that it is never caused by anything else. Among these observers is such an eminent authority as MacCallum who in his "Text-book on Pathology" states: "Our experience, which includes the study of an unusually large number of aneurysms, tends to impress us with the conviction that all are due to syphilis." Graves¹ in a study of forty-five aneurysms in autopsy material arrives at a similar conclusion. Medical text-books devote a great deal of space to the discussion of the relationship of syphilis to aneurysm, yet only a brief mention of the fact that other infections may perhaps be etiologic factors. It should therefore be both interesting and instructive to review this case of aortic aneurysm which has neither clinical earmarks nor pathologic evidence of syphilis.

REPORT OF CASE

M. W., a colored woman, experienced pain in the lower back immediately after her first childbirth. She was then seventeen years of age. The pain was severe and disappeared two or three months after the puerperium. Similar attacks of pain in the back, following childbirth and relieved after several months, occurred when the patient was nineteen, twenty, twenty-one and twenty-three years of age. However, following the birth of her sixth child when the patient was twenty-five years old, the pain in the back recurred without relief at the usual time interval. The pain continued with such intensity that she was compelled to enter a hospital in July, 1930. The diagnosis was hyperthyroidism and retroflexion of the uterus.

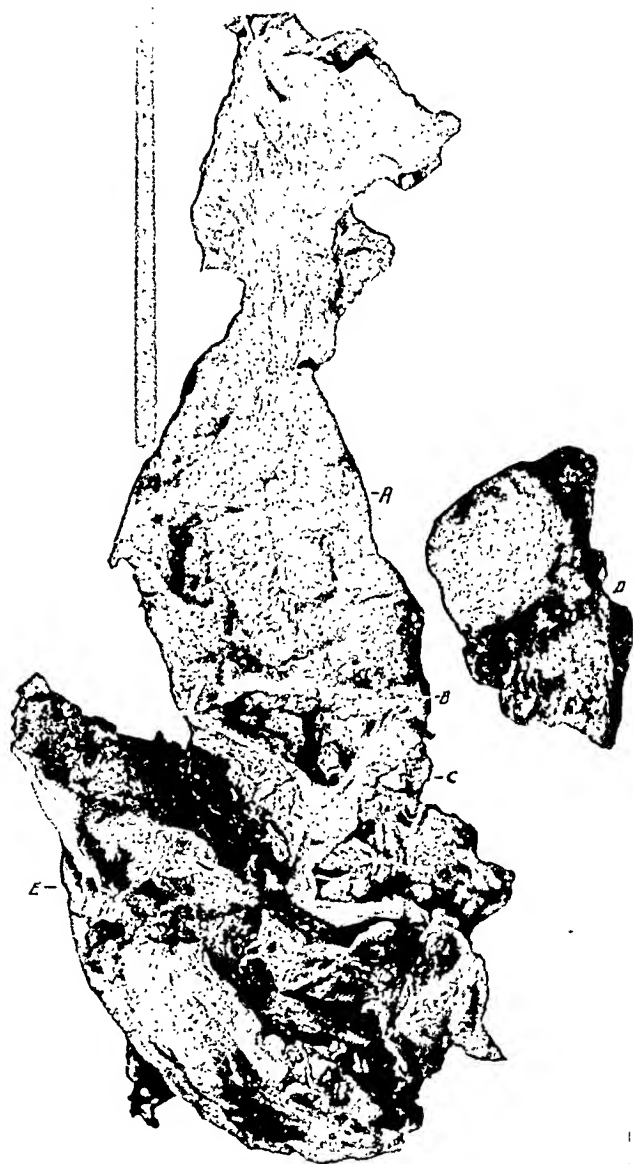


Fig. 159.—Intimal wrinkling is prominent in upper portion. *A* to *B*, first aneurysm; *B* to *C*, second aneurysm; *D*, thrombus from first aneurysm; *E*, retro-peritoneal hematoma.

twelfth dorsal and second lumbar segments and involves the celiac axis. Neither aneurysm has caused any erosion of the vertebral bodies.

because of severe vaginal bleeding. Examination revealed a seven months' pregnancy and a placenta praevia. A premature delivery by version under ether anesthesia was done. The baby died twenty-four hours later because of prematurity.

The patient's final admission to the hospital occurred on February 7, 1933. In the receiving ward it was noticed that the tongue was the seat of superficial ulcerations surrounded by definite white circinate borders. These were thought to be syphilitic mucous patches and the patient was assigned to the women's venereal ward. She was, however, soon transferred to the medical service of Dr. Truman G. Schnabel. Questioning disclosed that the tongue lesions had been present since early childhood, recurring from time to time and that the patient's mother and children all had similar tongue lesions. The pains now were higher in the back and under the shoulder blades. Physical examination at this time was no different than during the previous admissions except that a systolic thrill and a loud systolic bruit were present over the pulsating aorta immediately above the umbilicus. There was an unusually marked precordial heave in the absence of cardiac enlargement.

Further Laboratory Observations.—The Wassermann reaction of the blood was again negative. α -Ray of the cervical, thoracic and lumbar spines revealed no abnormalities. A chest α -ray showed considerable widening, elongation, and tortuosity of the descending aorta. Gastro-intestinal α -ray study was negative except that the esophagus was displaced anteriorly by the dilated aorta, however the act of swallowing was not interfered with.

Final Course.—The pain continued in spite of narcotics frequently administered. On March 31st, the patient complained bitterly of abdominal distention and flatus, but on examination no distention of the abdomen could be elicited. Five o'clock on the morning of April 1, 1933, the patient was found dead, having apparently died in her sleep.

Necropsy Report.—The following is a verbatim abstract from the necropsy report made by Dr. R. P. Custer.*

Gross Examination.—*Aorta.*—The ascending portion and arch are slightly dilated and show mild yellow atheromatous streaking; there is an occasional patch of intimal wrinkling that suggests luetic scarring. In the lower thoracic portion, extending from the eighth to eleventh dorsal segment, lies a saccular aneurysm that is 9 cm. in diameter and points ventrally; the lumen is filled with a white, dry, friable, laminated thrombus that is readily detached from the thin, fibrous wall. Beginning 1 cm. below this aneurysm, separated from it at the level of the diaphragmatic attachment by a narrow ridge, lies a second saccular aneurysm that measures 12 cm. in diameter, pointing ventrally and presenting a point of rupture at its ventral apex; from this point there has been extravasation of blood that has burrowed along the left renal artery, surrounding the left kidney with a mass of freshly coagulated blood; dissection has occurred between the leaflets of the mesentery, along the superior mesenteric artery, down to the attachment of the small intestine and in several places extending under the serosa of the bowel. This aneurysm lies between the

* To Dr. Custer I wish to acknowledge my gratitude for his ever courteous and helpful attitude, and especially for his painstaking labors in the study of these specimens.

scarred patches nor are they associated with inflammatory exudate of note. The internal elastic lamina is not demonstrable. The intima is greatly thickened, dense, in parts hyalinized; parallel rows of fibrocyte nuclei are prominent in the majority of the sections. The wrinkling seen grossly has been produced by folds of this wide intima; the convolutions bear no relation, however, to scars in the media; rather does it appear as an intimal hypertrophy without accommodation of the underlying media to the increased surface. There are occasional clefts in the intima, most prominent at the level of the subintima; some of these



Fig. 161.—Aorta ($\times 414$), showing bacteria within media at upper margin of first aneurysm.

contain short, plump rods and diplococci; at one point there is an inflammatory reaction of a subacute character to this bacterial colonization, indicating that it was present before death. At the edge of the first aneurysm this bacterial growth is very marked and is seen in all coats. One gains the impression that the aneurysms are not of syphilitic origin. The aorta shows marked degenerative changes in all coats; the relation of the bacteria as an exciting cause is open to question.

Thyroid is normal.

Histologic Description.—*Tongue.*—At each margin of the section the mucosa is comparatively normal; the majority of the included surface shows a marked hyperplasia of the stratified squamous epithelium which sends down penetrating pegs into the chronically inflamed and densely fibrotic submucosa. The inflammation is not of a character that would suggest lues, the cell exudate being predominantly lymphocytic and bears no relation to arterial channels.

Aorta.—Six sections, taken through arch, descending thoracic portion and in the region of each aneurysm, are examined; a rather uniform basic picture



Fig. 160.—Aorta ($\times 27$), showing extreme intimal thickening and wrinkling. (Section from upper thoracic portion.)

is seen in each. There is marked fibrosis of the adventitia that is exceedingly dense and hypocellular; many of the vasa vasorum show thickened walls that are not of the inflammatory, proliferative nature that one sees with lues and there is no cell reaction in their peripheries. The media is markedly degenerated and fibrotic, the elastic fibers being maintained in some portions, completely lost in others; where present they are broken and frayed. There is moderate vascularization of the media at some points but the vessels do not lie within

aneurysms caused by periarteritis nodosa are due to streptococci which cause an infection that spreads along the periaarterial lymphatics. Stengel and Wolferth also mention embolism as an intravascular cause of aneurysms but hasten to point out that the embolism is always associated with infection. Brindly and Schwab⁴ studied 100 cases of aortic aneurysm in autopsy material and found that 77 were due to syphilis, 9 to atheroma, and 2 to bacteria (mycotic). Twelve of these aneurysms they were unable to classify. The average age of their mycotic cases was twenty-eight.

Richey⁵ collected from the literature 41 cases of aneurysm of the thoracic aorta in persons not over eighteen years of age. Of these only 2 showed irrefutable evidence of syphilis, although each author considered carefully syphilis as a possible etiologic agent. One half of the cases were mycotic. Five of the cases had congenital anomalies of the aorta.

From these reports it becomes evident that in the young syphilis does not play the same rôle in the production of aneurysm as it does in the adult. More stress must be laid to streptococcal infections, to which the young are admittedly susceptible. We must bear in mind that the arteries of the young are as susceptible to the streptococcus virus as are the tonsils, the endocardium and the joints.

May we now theorize concerning the patient who is the subject of our clinic in the light of the above studies? Either because the infection from her repeated sore throats had involved the aorta or because of some congenital weakness of her aorta, or both, the stress of a normal labor at the age of seventeen was sufficient to cause a rupture of the intima of the aorta. This was the cause of her pain for several months. The same process with partial healing happened after the labors that occurred at the ages of nineteen, twenty, twenty-one, and twenty-three. Following her sixth labor, repair no longer took place and actual aneurysmal formation began and then continued. Such an explanation seems plausible based on the postmortem findings and is certainly more in keeping with the clinical facts than syphilis.

DISCUSSION

The patient died of a ruptured aneurysm at the age of twenty-eight after having had the symptom of pain in the back for eleven years following the stress of her first labor. Six of her children are living and well. The second child died of intestinal obstruction and the eighth child died because of prematurity, the patient having been delivered at seven months by version and under ether anesthesia because of a placenta praevia. During her eleven years of illness numerous Wassermann tests on the blood and spinal fluid were done and they were all negative. The only suspicion of syphilis aside from the question of aneurysm was the circinate lesions on her tongue. Obviously, they were not syphilitic. Syphilitic lesions of the tongue are rarely unaccompanied by hard and painless enlargements of the regional lymph nodes. She had no such enlargements. The clinical appearance, the chronicity, the hereditary nature, and the histologic findings all point to the diagnosis of geographic tongue, known also as Moeller's glossitis or chronic superficial glossitis. The etiology of this lesion is unknown, and it undoubtedly occurs in people for whom there is no suspicion of syphilis. Dr. Custer made special effort to find histologic evidence of syphilis but was compelled to conclude that such evidence does not exist in the postmortem tissues.

What then are the causes of aortic aneurysm other than syphilis?

In a very exhaustive manner Stengel and Wolferth² discuss the occurrence of "mycotic aneurysm of intravascular origin." Including 4 of their own cases, they have collected 217 such aneurysms from the literature of which 66 per cent were in the aorta, and 71 per cent occurred in the first thirty years of life. They state that aneurysms not due to syphilis or to other intravascular infection may be caused by trauma, arteriosclerosis, congenital defects of vessels, adhesions pulling the arterial walls outward (traction aneurysm), vascular tumors, chemical erosions (as in the walls of gastric ulcers or carcinomas), bacteria from adjacent structures (as in tuberculous or suppurative collections), and periarteritis nodosa. Klotz³ believes that the

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That toxic reactions occur after the use of novasurol has been known since its introduction. In using the drug as an antiluetic, Zieler,¹ in giving 5000 injections to 900 patients reported the following results: vomiting in 2.4 per cent of cases and 0.5 per cent of injections, diarrhea in 6 per cent of cases and less than 0.1 per cent of injections, stomatitis in 4 per cent of cases, kidney irritation in less than 1 per cent of cases, but only in those with previous evidence of renal disease.

Redlich,⁶ in 1925, reported a case of damage to the kidney attributable to mercury in a patient with tuberculosis who died four weeks after an injection of novasurol. Saxl⁷ quickly replied to this by claiming that the kidney damage in this case could not have been due to novasurol because of the length of time intervening between its use and the death of the patient. He also said that the drug had been contraindicated and should not have been given. Marvin,⁸ in 1926, reported that of 26 patients who received novasurol, 4 had moderately severe stomatitis and salivation, 2 had bloody diarrhea requiring the use of opium, and 1 patient went into an alarming collapse, appearing at the point of death for several hours. He concluded that novasurol should be given only to patients whose edema had failed to respond to theobromine or theophylline. Sprunt,⁹ in 1930, reported that of 9 cases who had received novasurol, 3 showed epithelial necrosis of the kidney attributable to mercury at autopsy. In 2 of these cases conditions which he considered contraindications to its use, viz., fever and active tuberculosis, were present, but in the third case there was no contraindication. Sprunt concluded that the administration of novasurol was justified as a last resort. Whitaker,¹⁰ in 1932, defined the contraindications to novarsurol as acute nephritis, acute enteritis, and chronic nephritis with nitrogen retention. He did not consider albuminuria and cylindruria in the presence of good kidney function as contraindications.

Animal experiments have tended to discount the toxicity of novasurol. Keith and Johnstone,¹¹ working on dogs, reported that repeated doses of novasurol over a five-month period in amounts corresponding to those used clinically produced no

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MERCURY POISONING FROM NOVASUROL IN HYPERTENSIVE HEART DISEASE

THE diuretic action of mercury has been known for over a hundred years. As far back as 1799, Ferriar made the observation that digitalis was more effective in reducing edema when given with calomel than when given alone. In Richard Bright's monograph on renal disease published in Guy's Hospital reports in 1836, he mentioned the use of calomel and other mercury compounds, but he concluded that they did more harm than good. Toward the end of the last century, in 1886, Jendrassik advised the use of repeated small doses of calomel to produce diuresis in cases of edema.

Novasural, a complex mercury-containing compound, chemically sodium oxymymercuric-ortho-chlorphenol-oxylacetate with diethylmalonylurea, was introduced by Zieler¹ in 1917 as an antisymphilitic. Its diuretic properties were discovered by Saxl and Heilig² in 1920 in the Wenckebach clinic in Vienna, and since their work it has been used only for this purpose. Novasurol has been used to reduce edema in a variety of conditions, the chief of which is congestive heart failure with anasarca and other signs of decompensation. A great number of reports concerning its usefulness as a diuretic in this type of case have appeared since 1920. Keith, Barrier and Whelan³ have advocated its use in some types of nephritis, particularly the nephrotic type. Others^{4, 5} have been successful in reducing ascites due to cirrhosis of the liver with novasurol. Still other conditions in which it has been successfully used to reduce abnormal collections of fluid are Banti's disease with ascites, Pick's disease, bilateral lymphedema of the legs following abdominal operation, and unilateral edema of the leg secondary to varicose veins.

bright red blood every ten to twenty minutes. He had intense abdominal pain and generalized abdominal tenderness and rigidity. It was believed the man had either an intussusception or an abdominal vascular crisis. He was transferred to the surgical service where laparotomy was performed under local anesthesia. At operation the cecum, ascending colon, and part of the ileum were found to be intensely congested and edematous. No evidence of mesenteric thrombosis was found. An ileostomy was performed, a catheter being sutured into the terminal part of the ileum. His condition during operation was very poor. He died the next day, September 11, 1932, at 8.40 p. m.

Necropsy was performed sixteen hours after death. The autopsy was limited to the abdomen through the surgical incision. The findings of interest were in the kidneys and the gastro-intestinal tract. The former showed, grossly, acute toxic nephrosis, arterionephrosclerosis, and acute passive congestion. The gross diagnoses were subsequently confirmed through microscopical examination. The mucosa of the stomach was congested and presented punctate hemorrhages. The duodenum was markedly inflamed with circumscribed focal hemorrhages about 5 mm. in diameter in the submucosa. The jejunum and ileum were comparatively free from lesions. Beginning at the cecum and extending throughout the entire colon, the mucosa was extremely hemorrhagic and degenerated, with patchy areas of actual necrosis. The lumen was filled with a cranberry-like material.

Qualitative tests for mercury performed on the kidney, the colon, and urine, were strongly positive.

The cause of death was given by the pathologist as hypertensive cardiovascular disease and mercury poisoning.

Case II.—S. T. colored, male, aged thirty-nine. The patient was admitted to the medical wards of the Philadelphia General Hospital three times. The first admission was on January 4, 1932, and the last was on June 30, 1932. On each admission he showed signs of congestive heart failure. His heart was markedly enlarged, extending to the left anterior axillary line. The systolic blood pressure varied between 190 and 220 mm. of mercury, and the diastolic between 130 and 170. Edema of the legs and ankles, hepatic enlargement, pulmonary congestion, and, on the last admission, right hydrothorax, were present.

The urine showed an occasional trace of albumin; a few hyaline and granular casts were found in only one of many examinations. The blood urea nitrogen varied between 13 and 20 mg. per 100 cc. The blood Kahn test was positive. The urea clearance test showed 60 per cent standard clearance in the first hour, and 54 per cent in the second.

On his last admission his condition grew steadily worse in spite of digitalization, and the administration of theocin. Venesections and repeated thoracenteses were also done. He was given a series of twenty mercury inunctions because of the positive Kahn test. By the first part of December, 1932, he had tremendous generalized subcutaneous edema, involving practically his entire body. Novasurol, 1 cc. of 10 per cent solution, was given intramuscularly on December 13th. During the next forty-eight hours his urinary output exceeded the fluid intake for the first time in many weeks. Subsequently his output diminished and he became increasingly edematous. He grew steadily worse and died at 5.15 p. m. on

functional change in the kidney of the dog. Later Johnstone,¹² in studying the comparative toxicity of novasurol and salyrgan in rabbits, found that novasural was only slightly the more toxic of the two, and that the difference in toxicity was not nearly as great as one would be led to expect from clinical reports.

The last edition of *New and Non-Official Remedies*¹³ includes novasurol, and states that, "Best results have been obtained in dropsies due to cardiac disease. While contraindicated in nephritis, it has been reported to be useful in nephrosis and glomerulonephritis. It is usually ineffective in ascites due to cirrhosis of the liver and Banti's disease, and may be harmful." The general impression gained from the literature is that if care is taken in selecting cases for the administration of novasurol, it is a useful drug, and serious toxic effects will not occur.

I now wish to report 2 cases of hypertensive heart disease with decompensation in which novasurol was given to produce diuresis. Neither of these cases had shown clinical evidence of kidney damage other than passive congestion associated with heart failure. In both cases death resulted, and necropsies showed that mercury poisoning was a contributory cause of death.

Case I.—B. K., white, male, aged thirty-eight. The patient was admitted to the medical wards of the Philadelphia General Hospital on August 31, 1932, complaining of shortness of breath, swelling of the legs, and cough. These symptoms had appeared six months prior to admission, and had been growing increasingly severe. He had been hospitalized in another institution during June, 1932, on account of the same symptoms.

The family and past medical histories were essentially negative. He gave no history of rheumatic fever or of a luetic infection.

On admission the patient was in a state of cardiac decompensation. The heart was enlarged to the left. No valvular lesion was detected. The blood pressure was 218/130 in millimeters of mercury. Pulmonary congestion, bilateral pleural effusions, hepatic enlargement, and edema of the lower extremities to the knees were present. The urine showed a cloud of albumin and 3-plus hyaline casts. The blood urea nitrogen was 24 mg. per 100 cc. on September 2nd, and 19 mg. per 100 cc. on September 5th. The blood Kahn reaction was negative.

Treatment consisted of digitalization, the administration of theocin and ammonium chloride, restricted fluid intake, and one venesection of 550 cc. The patient did not improve. On September 9th, as the peripheral edema and pleural transudates were increasing, 1 cc. of 10 per cent solution novasurol was given intravenously. Sixteen hours later he developed a severe bloody diarrhea, passing

total amount of mercury found exceeds the 33.9 mg. given in the novasurol is explained by the fact that the patient had received twenty mercury inunctions two months prior to death. In both cases mercury poisoning was regarded by the pathologists as a contributory cause of death.

Discussion.—Clinically the two patients reported were cases of hypertensive cardiovascular disease without signs of kidney damage other than passive congestion. Necropsy findings confirmed the clinical diagnosis. The kidneys at autopsy showed, aside from the acute toxic nephrosis which was attributed to mercury, only passive congestion and the nephrosclerosis that is to expected in hypertension. Previously defined renal contraindications to novasurol, viz., acute nephritis, or chronic nephritis with nitrogen retention, were therefore not present in these cases from either a clinical or a pathologic standpoint. Nevertheless these kidneys were unable to withstand even a single dose of novasurol, and extensive and severe hemorrhagic changes in the kidneys and gastro-intestinal tract resulted. It is therefore evident that the nephrosclerotic changes present in hypertensive cardiovascular disease are sufficient to contraindicate the use of novosurol in this type of heart disease.

Conclusions.—1. Single doses of novasurol can produce severe hemorrhagic gastrocolitis and tubular necrosis of the kidney.

2. Mercury poisoning following a single dose of novasurol can be a contributory cause of death.

3. Hypertensive heart disease, because of the associated nephrosclerotic changes, is a contraindication to novasurol.

NOTE: Grateful acknowledgment is made to Drs. R. G. Torrey, P. A. McCarthy, and T. G. Schnabel for their permission to use these cases; to Drs. R. P. Custer and E. Bevan who performed the autopsies; and to Mr. A. Hunsburger, Jr., who did the chemical analyses.

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December 19, 1932, six days after receiving novasurol. During this time he had no symptoms referable to the gastro-intestinal tract.

Autopsy was performed twenty-four hours after death. The important findings were as follows: The heart weighed 600 Gm. and was enlarged in all directions, the left ventricle in particular showing tremendous hypertrophy. On cut section the kidneys appeared so congested that the pyramids stood out prominently, appearing almost black. The cortex was also markedly congested. The gross diagnoses were acute nephrotic nephrosis, acute passive congestion, and arterio-arteriolar sclerosis. These diagnoses were subsequently confirmed by microscopical examination. The stomach contained a reddish-brown fluid which when washed away showed a mucous membrane so hemorrhagic as to appear bright crimson. The mucous membrane of the duodenum was also extremely hemorrhagic. Some hemorrhages were found in the mucous membrane of the small intestine, and the mucosa of the large intestine was as hemorrhagic as that of the duodenum and stomach.

The cause of death was given by the pathologist as hypertensive cardiovascular disease with decompensation and mercury poisoning.

Subsequent quantitative examination of various organs for mercury gave the following results:

	Mercury found per 100 Gm. of wet tissue.	Mercury found in whole organ (calc.).
Stomach.....	0.7 mg
Kidney.....	8.8 "	28.0 mg.
Liver.....	4.5 "	48.5 "
Intestine.....	0.6 "

Comment.—Each of these two patients received 1 cc. of 10 per cent solution of novasurol, containing 33.9 mg. of mercury. One patient (Case II) had a moderate diuresis, the other did not. One (Case I) developed a severe bloody diarrhea and such marked abdominal pain that he was thought to have had a mesenteric thrombosis or an intussusception, and laparotomy was performed. The other had no symptoms referable to the gastro-intestinal tract. It was a complete surprise, therefore, when Case II as well as Case I showed at necropsy hemorrhages in various portions of the gastro-intestinal tract. Tubular necrosis of the kidney was present in both cases, and this as well as the hemorrhagic gastrocolitis was considered by the pathologists as a sign of acute mercury intoxication. In Case I, mercury was found in the kidney, urine, and colon by qualitative tests. In Case II quantitative tests for mercury were performed on the kidney, stomach, intestine, and liver. The highest concentration of mercury was in the kidney. That the

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critical points in erythrocyte development according to Sabin. Her emphasis on these critical points from the standpoint of

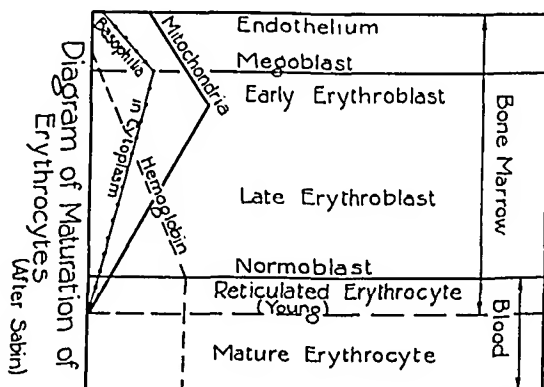


Fig. 162.—Diagram of maturation of erythrocytes (after Sabin).

histology is most significant clinically as will be seen later in the discussion of certain specific factors in blood regeneration.

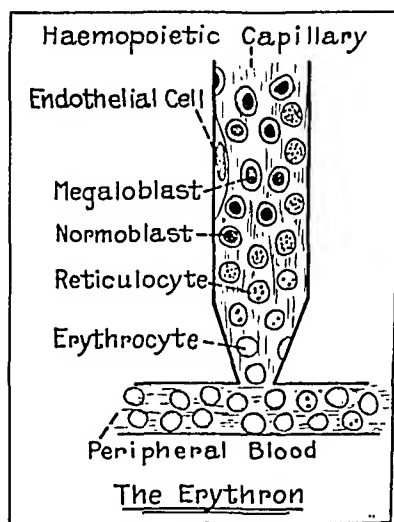


Fig. 163.—Diagram to indicate the regeneration of erythrocytes (after Witts).

Witts² well illustrates erythrocyte development graphically as shown in Fig. 163. After reaching maturity in the marrow,

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**CLINICAL FACTORS IN THE PRODUCTION OF ANEMIA
AND THE REGENERATION OF ERYTHROCYTES AND
HEMOGLOBIN**

RUSSELL L. HADEN

THE erythrocytes in the blood of man are constantly being destroyed and replaced. The life span of a circulating red blood cell is only two to six weeks and the erythrocyte count in health is very constant, so the entire mass of cells must be renewed often. The regeneration of erythrocytes and hemoglobin normally just compensates for the cells lost. An anemia is due to a loss of the normal balance between blood formation and blood destruction. The various factors concerned in the development and cause of an anemia must be considered in relation to the life of the erythrocyte.

THE LIFE HISTORY OF ERYTHROCYTE

The erythrocyte develops intravascularly from endothelium lining the capillary spaces in the bone marrow. The stages in formation are: (1) The endothelial cell, (2) the megaloblast, (3) erythroblast, (4) the normoblast, (5) the reticulocyte and (6) the erythrocyte (Fig. 162). Each circulating erythrocyte is not derived from a single endothelial cell since cell division occurs in the marrow at all stages and is most active at the normoblast level. Sabin¹ states that 99 per cent of the cells of normal marrow are erythroblasts and normoblasts. Very few megaloblasts are found, although active division occurs also at this stage. The megaloblast and the normoblast stages are the two

factor of liver is necessary for the development and maturation of the megaloblast. In the absence of this factor the marrow becomes crowded with megaloblasts at the expense of normoblasts, and most of the cells released are abnormal in size, shape and hemoglobin content. Iron and possibly other substances are necessary for normal hemoglobin formation. In the absence of sufficient iron the erythrocytes are not only deficient in hemoglobin but also fail to attain normal size. Just as vitamins must be added to protein, fat and carbohydrate to assure normal growth and life of all animals, these special factors are necessary for normal red-cell development. It is most probable that time will reveal factors equally as necessary as those already known.

We should think of the erythrocytes of the bone marrow and circulating blood as a single organ. For this the name erythron has been suggested.² The total volume of this organ is twice that of the liver. It is subject to such changes as may influence all organs. Since it is labile, part may be lost by acute hemorrhage; it may be affected by congenital abnormalities (congenital hemolytic jaundice, sickle-cell anemia); a portion of the cells making up the organ may be destroyed (venom poisoning); the activity of the constituent cells may be depressed by cachexia and other influences; it is subject to deficiency diseases, just as other organs are.

LABORATORY STUDIES NECESSARY IN ANEMIA

1. **Icteric Index.**—This is the simplest measure of the bilirubinemia. The serum or plasma is compared with a dilute solution of *potassium bichromate*. The test is accurate, provided other pigments of similar color, such as carotin, are not present. A quantitative van den Bergh test may also be employed. The normal icteric index is 4 to 6.

2. **Reticulocyte Count.**—This is done by vital staining with brilliant cresyl blue. The normal count is 0.5 to 1.5 per cent.

3. **Determination of the Size of the Erythrocyte.**—The actual volume, or the volume index which indicates the volume

the cells are fed into the blood stream at the rate of 600 million to 2 trillion each day. The nucleus is lost before emergence and the vital staining granules disappear from all except a few cells. After fulfilling their function in the blood stream for two to six weeks the cells undergo fragmentation.³ The particles of fragmented cells are picked up by the reticulo-endothelial cells and dissolved. The hemoglobin set free is broken up into hematin and globin and hematin is changed into bile pigment after the iron has been split off.

Since bile pigments seemingly come only from hemoglobin, the amount of these pigments formed is a measure of blood destruction. With rapid destruction in the body, the amount of bile pigments in the circulation increases, urobilin appears in the urine and the stools contain more than the normal amount of pigments. Unless blood regeneration keeps pace with the increased blood loss an anemia develops. In the absence of liver disease or biliary obstruction, the amount of bile pigment in the plasma is the best clinical index of the intensity of blood destruction.

It is equally important to measure the rate of regeneration of erythrocytes and hemoglobin. A rise in erythrocytes and hemoglobin is definite evidence of bone marrow activity. The most sensitive indicator, however, is the relative number of reticulated erythrocytes in the blood, since these cells increase before the rise in the level of cells as determined by total counts. Other evidences of marrow activity are basophilia and nucleated red cells, leukocytosis and thrombocytosis. These may be spoken of as quantitative indicators of marrow activity. There are also definite indicators of qualitative changes in the marrow. These are macrocytosis and microcytosis, changes in shape, and in relation of thickness to diameter, hyperchromia and hypochromia.

Numerous elements are required for the growth and maturation of red cells. The fully developed cells contain proteins, iron and other mineral salts, carbohydrates, lipoids and water. In addition to these known substances, other elements are necessary, the exact nature of which is not clear. The antianemic

(1) Idiopathic hypochromic microcytic anemia (primary gastric defect leading to faulty assimilation of iron?).

(2) Other types of hypochromic and usually microcytic anemia as chronic hemorrhage, diets deficient in protein and iron, and disease or absence of the stomach.

It is evident that the first two divisions represent increased loss of blood either mechanically or by excessive hemolysis. The latter two divisions are caused by decreased blood formation. The first two represent quantitative decreases in the erythron; the third a quantitative decrease or a depression of activity; the fourth is due primarily to qualitative changes in the marrow.

DIFFERENTIATION OF FACTORS PRODUCING AN ANEMIA

The recognition of the different types of anemia depends on the proved correlation of clinical observations and laboratory studies. The important laboratory findings and course in the different types of anemia may be summarized as follows:

1. **Anemia Due to Acute Hemorrhage.**—When the blood volume is restored after a hemorrhage the cells are decreased in number but otherwise normal. Soon there is an outpouring of cells from the reserve supply in the marrow and spleen. Some are young so the reticulocyte count rises. Basophilia and nucleated cells are not seen unless the hemorrhage is very large. After a massive hemorrhage, an iron-deficiency type of anemia may develop. Unless the need for blood exceeds the reserve supply, the marrow in the long bones remains yellow.

2. **Anemia Caused by Excessive Hemolysis.**—Here the characteristic finding is a great increase in the end-products of hemoglobin destruction. The bile pigments in the plasma are increased and the stools are highly colored because of increased urobilin. If there is sufficient bone marrow, it attempts to compensate for the chronic blood loss by greater activity as shown by an increase in reticulocytes, basophilia and nucleated cells. The marrow in the long bones becomes red if the hemolysis continues. The degree of anemia is determined by the balance of the two processes.

of the average of the number of red cells. The
difference may be due to the fact that the number of red cells
from the blood is not constant.

4. Depression of the hemoglobin content in the
cells in the blood.

5. Qualitative changes in the hemoglobin in the
erythrocytes.

6. Changes in the number of reticulocytes.

7. Special blood examinations for the presence of
gastric analysis and for the presence of parasites.

The results of the blood examination may be used in
diagnosing anemia.

CAUSES OF ANEMIA

The factors which cause anemia may be divided into two
categories: (a) Primary, and (b) Secondary.

1. Primary Anemia.—(a) Idiopathic anemia, from
the history.

2. Inherited Anemia.—(a) Sickle cell anemia, a con-
genital hereditary disease of the red cells.
(b) Thalassemia, a congenital disease of the
red cells.

(c) Secondary anemia, from various causes, certain
bacterial infections, and from the use of certain
drugs.

3. Depression of Erythropoiesis.—(a) Idio-
pathic aplasia, a disease of the bone marrow.

(b) Disorders of the bone marrow, such as leukemia,
as lead or arsenic poisoning, or the use of certain
of metabolic poisons, such as alcohol, disturbance
of marrow function, or the use of certain substances, infiltration
of marrow by tumor cells, or the use of certain poisons.

4. Deficiency of Essential Substances Necessary for
Normal Erythropoiesis.—(a) Deficiency in produc-
tion or absorption of iron, (b) Deficiency in produc-
tion or absorption of folic acid, (c) Deficiency in produc-
tion or absorption of vitamin B₁₂, (d) Deficiency in produc-
tion or absorption of vitamin B₆, (e) Deficiency in produc-
tion or absorption of vitamin C, (f) Deficiency in produc-
tion or absorption of vitamin E, (g) Deficiency in produc-
tion or absorption of vitamin K, (h) Deficiency in produc-
tion or absorption of vitamin A, (i) Deficiency in produc-
tion or absorption of vitamin D, (j) Deficiency in produc-
tion or absorption of vitamin B₁, (k) Deficiency in produc-
tion or absorption of vitamin B₂, (l) Deficiency in produc-
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tion or absorption of vitamin B₉, (p) Deficiency in produc-
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tion or absorption of vitamin B₁₈, (y) Deficiency in produc-
tion or absorption of vitamin B₁₉, (z) Deficiency in produc-
tion or absorption of vitamin B₂₀.

(1) Iron deficiency.

(2) Other causes, such as sprue, pregnancy or fish
tapeworm infestation.

(b) Deficiency in the utilization of iron and possibly
other substances necessary for hemoglobin formation.

(a) *Deficiency in the Antianemic Factor Found in Liver.*—Pernicious and other closely related anemias are caused by a deficiency of this substance. The anemia is usually severe, the marrow is red in the active stages of the disease, and the bile pigments are increased in the plasma. Castle⁵ has shown that something is secreted by the stomach which acts on a substrate to form a substance specifically necessary for normal blood formation. A deficiency in formation or absorption of this substance leads to a characteristic type of anemia. In pernicious anemia there is a defect in the stomach secretion; in sprue probably a lack of absorption although both factors often are operative.

The deficiency in this antianemic substance leads to a very characteristic blood picture. The red cells are unable to mature properly from the megaloblast to the normoblast stage. The cells in the circulation are larger than normal. The marrow of the long bones is red and active but the cells can not mature normally on account of the specific deficiency. Many cells die in the marrow so there is an excess of bile pigment in the plasma, iron in the tissues and urobilin in the feces. Cells are being formed in the marrow but not released into the circulation.

The characteristic blood finding is a macrocytosis of the red cells. The volume and diameter are increased as well as the thickness. Poikilocytosis is common but the macrocytosis, best shown by the increased volume index, is the pathognomonic finding. The reticulocyte count is low in the active stages of the disease.

The specific deficiency may be permanent as in pernicious anemia or temporary as in pregnancy or sprue.

(b) *Deficiency in Iron and Other Substances Needed for Hemoglobin Regeneration.*—A chronic deficiency in the supply of iron resulting from increased loss, as in chronic hemorrhage, from deficient intake or absorption, or from some dysfunction of iron metabolism leads to a characteristic anemia. Iron is necessary for hemoglobin formation and also influences cell growth and division, especially at the normoblast stage. There

The iron set free in the destroyed hemoglobin is again used so no iron deficiency should develop. The other materials needed for cell building are also used over and over so there is no element of deficiency unless other factors are operative. Typically in this condition, the red cells show little change in volume and hemoglobin content although reticulocytes tend to be larger than normal so that the volume index may show some increase due to the high reticulocyte count. In congenital hemolytic jaundice the diameter of the cells is decreased while the thickness is increased.

3. Anemia Resulting from Depression of Bone-marrow Function.—In this condition there is a quantitative decrease or lessened activity of the red-cell building tissues. The defect is quantitative, producing varying degrees of anemia. Such cells as are formed are normal. The characteristic findings are a decrease in reticulocytes and absence of basophilia and other evidences of regeneration. The icterus index is low. The volume index and color index usually are normal. In idiopathic aplastic anemia, since the cells tend to revert to the embryonic type, the average cell volume may be slightly increased. The leukocytes and thrombocytes as well as the red cells are typically decreased. The marrow in the long bones is always yellow and in the flat bones also in idiopathic aplastic anemia.

4. Anemia Due to a Deficiency in Specific Substances Necessary for Normal Blood Formation.—In this group the qualitative deficiency in stroma- and hemoglobin-building materials is the important factor. Some special element needed for the growth of erythrocytes and for emergence into the blood stream is lacking. The condition is analogous to nutrition experiments in which protein, fat, and carbohydrate are abundant but one or more vitamins are deficient or missing.

Usually there is an overdevelopment of the marrow so it appears grossly red in the long bones. The cells do not reach the circulation in normal numbers since something is lacking to prepare for the final exit. Such cells as do reach the blood stream are abnormal. Two such deficiencies are definitely known and there are probably others as yet unrecognized.

TABLE 1
TYPICAL BLOOD FINDINGS IN VARIOUS TYPES OF ANEMIA

Anemia due to.	Type of bone marrow.	Icterus index.	Mean volume of erythrocyte (volume index).	Mean hemoglobin content of erythrocyte (color index).	Reticulocytes.	Nucleated cells and basophilia.
I. Acute hemorrhage	Yellow in long bones.	Low.	Normal.	Normal.	Slightly increased.	None.
II. Excessive hemolysis	Red in long bones.	Much increased.	Variable, usually slight increase.	Variable, usually	Increased.	Present.
III. Depression of bone marrow:						
1. Idiopathic aplastic anemia	Yellow in all bones.	Low.	Normal.	Normal.	Absent.	None.
2. Diminished marrow function due to other causes	Yellow in long bones.	Low.	Normal.	Normal.	Low.	None.
IV. Specific deficiencies:						
1. Deficiency in specific anti-anemic factor found in liver	Red in long bones.	Increased.	Much increased.	Much increased.	Low.	Slight.
2. Deficiency in iron	Red in long bones.	Very low.	Much decreased.	Much decreased.	Low.	Slight.

is only a small reserve of iron in the body, so a negative balance leads quickly to anemia.

In this iron-deficiency type of anemia there usually is little or no reduction in the total number of circulating cells, although the hemoglobin is decreased. The characteristic blood findings are small cells both in volume and diameter, and decreased hemoglobin content. Only the color index may be low but usually the cells are small also so that the volume index also is decreased. The microcytosis and the hypochromia are the characteristic findings. Red-cell destruction is less than normal

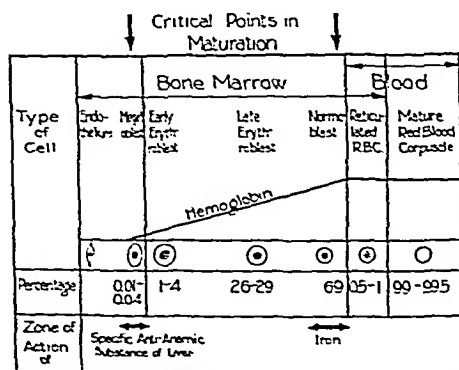


Fig. 164.—Diagram to show the points of action of iron and specific anti-anemic factor of liver. (After Sabin.)

so the icterus index is low. The bone marrow is red since it is more active than normal in an attempt to compensate for the release of the small cells deficient in hemoglobin. The cells are released rapidly but have not attained growth and hemoglobin. The factors in blood formation affected by the specific deficiencies are illustrated in Fig. 164.

I have summarized in Table 1 the characteristic blood findings in the four great groups of anemia. Not uncommonly a patient may suffer from an anemia produced by more than one factor.

TREATMENT

It is apparent that proper treatment depends on the proper recognition of the cause of the anemia. The cause of hemor-

missing substance by the use of liver, stomach tissues and liver extracts.

Likewise anemia resulting from a deficiency in iron is most satisfactorily treated if the deficiency is recognized and iron is supplied in adequate doses.

The treatment of every anemia depends on (1) the removal *or treatment of the cause*, (2) the proper use of diet and other general measures such as rest, (3) the intelligent application of liver and liver substitutes and (4) the use of iron. With every patient the cause must be removed or treated, if possible, and proper general measures instituted. It is especially important, however, to use liver and liver substitutes and iron in the proper cases. Macrocytosis is the characteristic finding in the blood of patients deficient in the specific antianemic factor of liver, and microcytosis and hypochromia of those with an iron deficiency. Hence, by classifying the anemia from the standpoint of cell size and hemoglobin content, one gets an excellent idea of the treatment indicated. This may be illustrated by Fig. 165.

SUMMARY

The entire mass of circulating red blood cells is replaced every two to six weeks.

The stages in blood regeneration and destruction and the factors influencing them are well known.

In studying a patient with anemia certain laboratory studies are necessary to detect the type of anemia.

The four important clinical factors are (1) acute hemorrhage, (2) excessive hemolysis, (3) depression of bone-marrow function and (4) a deficiency in specific substances necessary for blood formation.

The characteristic laboratory findings in the different groups of anemia are outlined.

The treatment depends primarily on the recognition of factors producing the anemia.

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rhage must be detected and adequately treated. Hemolytic agents must be eliminated. In congenital hemolytic jaundice the primary defect is in the red cell itself. This cannot be changed, but after splenectomy, crippled erythrocytes are not so easily removed from the circulation and hence an anemia does not develop so readily as before the removal of the spleen.

In primary aplastic anemia, no cause is known for the changes in the marrow. There is much to suggest that some-

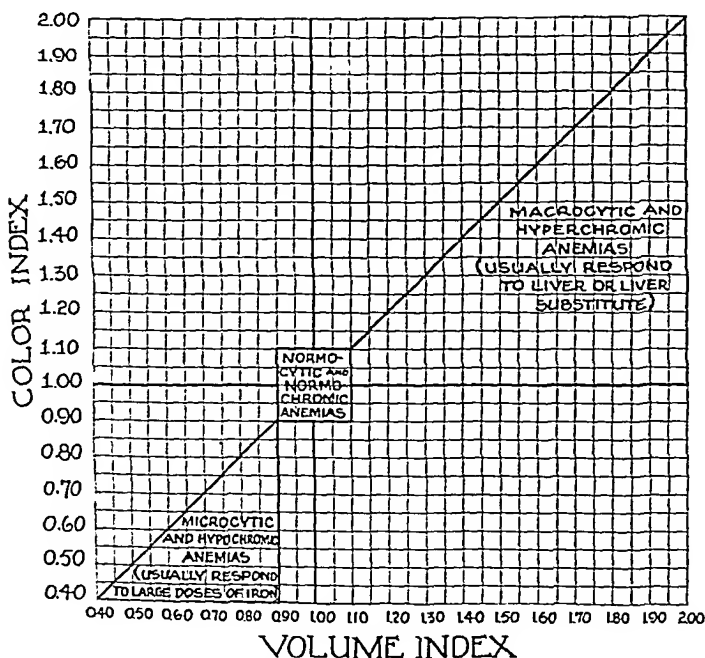


Fig. 165.—Relation of size and hemoglobin content of erythrocytes to treatment.

thing may be lacking for the normal change of endothelial cells to megaloblasts, but so far nothing specific is known and treatment is of little avail. Often the defects responsible for a depression of function, as myxedema, lead poisoning, or infection may be found and remedied. Too often the defect cannot be permanently removed as in chronic nephritis or leukemia.

Fortunately the defect responsible for pernicious and other macrocytic anemias can be remedied by replacement of the

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acterized by symmetrical involvement of the joints (especially of the smaller joints, such as the fingers), exhaustion, frequent evidence of impaired circulation to the extremities, anemia, pain, often a low-grade fever, and large effusions. It occurs at any age, but is more common before forty-five; it is more frequent in women and in the asthenic patient.

There has been much discussion in recent years concerning the etiology of chronic atrophic (rheumatoid) arthritis, yet there is no unanimity of opinion concerning all the causative factors. Many workers think that this is simply a bacterial disease and should be designated chronic infectious arthritis. The streptococcus has usually been considered the etiologic agent and numerous "specific" streptococci have been described, no two of which seem identical. The frequent association of chronic focal infection with chronic atrophic arthritis, the finding of organisms in the blood and joint tissues in some patients and the recent demonstration of agglutinins for hemolytic streptococci in the blood serum of patients suffering from the disease are strongly suggestive that bacteria play an important rôle in its causation. Studies of the micropathology of the disease as well as many of the clinical features suggest that chronic atrophic (rheumatoid) arthritis has much in common with rheumatic fever. It is most probable that the joint disease represents a reaction of the joints to a group of streptococci rather than to any one specific organism. It seems quite probable also that the joint reaction is not due to the presence of bacteria in the joint tissues but represents an allergic or other pathologic response to the presence of streptococci in some distant part of the body. Only time and further study will settle these moot questions.

There must, however, always be more than the one factor, the presence of bacteria, in the clinical development of the disease. Possibly the disease cannot develop in the absence of bacteria but the presence of bacteria alone is insufficient in most cases to produce the disease, so other factors are of equal or greater importance in the study and treatment of this type of arthritis. The frequent recurrence of rheumatic fever after all

THE STUDY AND TREATMENT OF CHRONIC (RHEUMATOID) ARTHRITIS. ONE ILLUSTRATIVE CASE

RUSSELL L. HADEN

IN studying a patient suffering from chronic arthritis it is necessary first to determine the nature of the primary pathologic process in and around the joints. The demonstration by Nichols and Richardson¹ of two entirely different pathologic changes in chronic arthritis, namely, primary degeneration of joint cartilage and primary proliferation of synovial membrane is accepted by all students of joint disease. The first leads to the clinical and radiographic picture of chronic hypertrophic arthritis (osteo-arthritis) and the other to chronic atrophic (rheumatoid) arthritis.

The degenerative type of chronic arthritis (chronic hypertrophic arthritis or osteo-arthritis) is a disease of age and use. It occurs to some extent in every elderly individual and usually is associated with other degenerative processes, such as arteriosclerosis. Ankylosis of the joints never occurs and rarely is this a disabling disease except in patients of advanced age, although it frequently is a source of discomfort. While chronic hypertrophic arthritis may almost be regarded as a normal aging process, the rapidity of development and the period of life at which it manifests itself clinically are much influenced by infections and other intercurrent disease, trauma, toxemia from various causes, circulatory disturbances, and glandular insufficiency or imbalance.

Chronic atrophic (rheumatoid) arthritis, on the other hand, never occurs normally, and is often a malignant disease. If unchecked, it usually ends in ankylosis of joints and other crippling deformities. All too often this type of chronic arthritis results in a "wheel-chair" disability. Chronic atrophic arthritis is char-

the entire joint. Six months later, her ankles had become swollen, painful and stiff and psoriasis had appeared on the feet. The disability in these joints had persisted and two years before admission the elbows and shoulders had become involved and psoriasis had appeared in these areas. The neck had been affected for one year, and the wrists and fingers for six months. The nails of both fingers and toes had been markedly thickened by the psoriasis.

The tonsils had been removed and all suspicious teeth had been extracted. No other infection had been found. The patient had tried many different types of treatment, including injections of a specific vaccine for one year. No treatment had given any relief. For several weeks before coming to the clinic, the patient had been confined to her bed.

Family History.—The patient's father, mother, two brothers and one sister were living and well. The father had had mild psoriasis. There was no history of diabetes, arthritis, vascular disease or tuberculosis in the family. She had never been pregnant.

Past History.—The patient had had measles, whooping cough, chickenpox, and diphtheria in childhood. She gave a history of frequent attacks of tonsillitis as a child with one attack of quinsy before tonsillectomy in 1916. When she was sixteen years of age, she was considered to be anemic. A suspension of the uterus had been done in 1908 and a hysterectomy in 1929. She seldom had headaches. There was no history of known dental or sinus infection or of sore throat in recent years. The cardiorespiratory history was entirely negative. She had always been constipated and had some flatulence but complained of no indigestion. For a number of years she had had nocturia (two or three times). The menses had appeared at the age of fourteen and had been regular, though scanty, before the hysterectomy. The patient thought her diet always had been good; she ate fruit and vegetables in abundance. For the last three months, she had eaten no meat, sweets or bread. She slept well and did not use tea, coffee or tobacco. Her normal weight had been about 160 pounds. Recently she had weighed 170

foci are removed is repeatedly observed and it is a common experience to see patients who have had all demonstrated foci of infection removed without influencing the course of chronic atrophic arthritis. We should think of the clinical expressions of the disease as representing a loss of balance between resistance and infection, in which many factors may be involved. It is one thing to demonstrate a specific etiologic factor in a disease and another to determine the factors which enter into the clinical development of a disease. The tubercle bacillus is a requisite and sole etiologic agent in tuberculosis but many factors determine the development of the clinical picture of pulmonary tuberculosis. We think of every adult as having viable tubercle bacilli in the body, the activity and development of which are dependent on numerous factors. Likewise, the treatment of tuberculosis does not resolve itself into the use of vaccine made from the tubercle bacillus. The reservation should also be made that the disease may perhaps develop entirely apart from bacterial infection, due to some deficiency, toxemia or disturbance of the sympathetic nervous system. Time only will determine whether there is a single specific causative factor in chronic atrophic (rheumatoid) arthritis, but the lack of proof of a specific infecting agent only emphasizes the need for studying more completely every patient suffering from all forms of arthritis for all possible factors in the clinical picture of the disease. Even with specific bacterial infections there are always nonspecific factors. Successful treatment of a patient depends almost entirely on a careful preliminary study.

I have selected the following case history to illustrate the study and treatment of the severer form of chronic atrophic arthritis.

Case History.—A married housewife, aged forty-seven years, was admitted to the Cleveland Clinic, September 14, 1932, complaining of arthritis, constipation and psoriasis.

Present Illness.—The patient stated that she had been well until six years before admission, when she had begun to have some stiffness in the knee. At the same time, an area of psoriasis had appeared on the right knee and gradually had spread over

ach and duodenum were normal. The colon, especially on the right side, was very large and atonic (Fig. 166).

Treatment.—The patient was kept in bed and for the first five days in the hospital was allowed to eat only fruit juices. The diet for the rest of her stay was low in carbohydrates and



Fig. 166.—Colon of patient after barium enema on admission. Note the size and absence of haustra.

high in vitamins. The caloric intake was kept low (1200 calories). Protein was not restricted. Vitamins were added as halibut liver oil, vegex and wheat germ.

Physiotherapy was given daily. Sun baths were given when possible, and ultraviolet radiation, when there was no sunlight.

pounds. The patient's husband was a successful banker, her home life was happy, and she had not been limited in treatment in any way by financial or other handicaps.

Physical Examination.—The patient was in a good state of nutrition. Her weight was 146 pounds, which was 15 pounds overweight for her age and height. The tonsils had been cleanly removed and the teeth were in excellent condition. The thyroid gland was just palpable. The examination of the heart, lungs, abdomen and pelvis showed nothing significant. The blood pressure was 140 systolic, 70 diastolic, and the pulse rate was 90. The reflexes were normal. There were large patches of psoriasis on the scalp, abdomen, back, elbows, knees, feet, and hands. The nails of the fingers and toes were greatly roughened and thickened.

Joints.—There was limitation of motion and stiffness of the neck and shoulders. The elbows could not be fully extended. The knees were swollen and stiff. Flexion of the wrists was much impaired. The fingers and toes were swollen and tender to touch. There was little redness. The spine and hips were free.

Special Examinations.—The sinuses were clear on transillumination and no remnant of tonsil tissue could be seen. The dental roentgenograms showed no pulpless or suspicious teeth.

Laboratory Studies.—The urine was constantly negative, except for a trace of albumin at times. The blood count showed 5,320,000 red cells, 71 per cent hemoglobin, color index 0.66, white cell count, 8,250; differential count, neutrophils, 73 per cent; lymphocytes, 25 per cent; and eosinophils, 2 per cent. The basal metabolic rate was minus 14 per cent. The gastric analysis revealed 3 degrees free acid, and 8 degrees total acid. The sedimentation rate of the red corpuscles was 78 mm. in one hour (Westergren method). The blood sugar was 92 mg., uric acid, 5.1 mg., and urea, 27 mg. per cent. The blood Wassermann reaction was negative.

Roentgenograms.—A radiograph of the hand showed marked atrophy of bone without changes in the cartilage. The Graham-Cole test showed a poorly functioning gallbladder. The stom-

and 89 per cent hemoglobin. The blood sugar, urea and uric acid were within normal limits. New normal nails were appearing. A roentgenogram following a barium enema showed a remarkable improvement in the tone of the colon. The right



Fig. 168.—Colon of patient three months after beginning treatment. Note the great decrease in size due to better tone.

colon was no longer dilated, the left was narrow and smooth (Fig. 168).

The patient returned again six months after leaving the hospital. She had gone back to her normal activities. The joints were entirely normal. No trace of the psoriasis remained and the nails were normal. The sedimentation rate of the corpuscles

Hot paraffin baths were used for the hands and diathermy for the other involved joints. Breathing exercises and abdominal massage also were employed.

The medication consisted of seven injections of neoarsphenamine, 0.3 Gm. twice a week, Blaud's pills, 60 grains each day, dilute hydrochloric acid and 1 grain of thyroid extract twice a day. For a short time, small doses of insulin were given to stimulate the appetite. The psoriasis was treated by local applications. Five injections of typhoid vaccine were given intravenously after two weeks' preliminary treatment.

Course in Hospital.—The patient showed gradual but steady improvement. The psoriatic lesions became smaller, the joints were less swollen and painful, and there was a gradual loss in weight. The low-grade fever (Fig. 167) disappeared

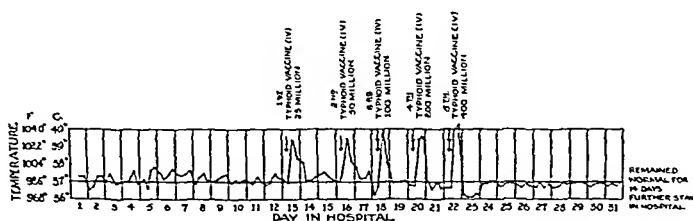


Fig. 167.—Temperature chart of patient. Note the daily fever and return of temperature to normal after injection of typhoid vaccine.

entirely after the injections of typhoid vaccine. The blood uric acid returned to normal. The blood count showed little change. The color index remained low. The sedimentation rate of the red cells was 57 mm. after four weeks' treatment and 43 mm. six weeks after admission. The basal metabolic rate rose to minus 6 per cent. The patient was discharged from the hospital after six weeks.

Further Study.—The patient returned one month later for a check-up. The treatment instituted at the hospital had been continued. The joints were symptom-free and showed no swelling. The psoriasis had almost entirely disappeared. The weight was now 136 pounds. The sedimentation rate of the red cells was 36 mm. and the blood count showed 5,240,000 red cells

valuable. Gallbladder disease or disturbed function may be revealed by a dye visualization test. The size and shape and emptying rate of the colon are determined by the radiographic study after a barium enema. Changes in the colon may give definite indications for treatment. A gastric analysis should always be done. In many cases of chronic atrophic arthritis, there is achylorhydria, which may throw light on other findings, such as hypochromic anemia.

5. *Careful routine blood studies* frequently reveal indications for treatment. Hypochromic anemia, often with hypochlorhydria or achlorhydria, is a frequent finding in chronic atrophic (rheumatoid) arthritis. This type of anemia may be treated specifically with iron in large doses. Relief of the anemia usually influences the course of the disease materially.

6. *Certain blood chemical studies* are always indicated. A glucose tolerance test affords valuable information. Many patients show a curve of decreased tolerance characteristic of diabetes mellitus which, with relief of the joint disease, may return to normal. The finding of such a curve is an indication for carbohydrate restriction in the diet and sometimes for the use of insulin.

The blood uric acid should also be determined, especially in chronic hypertrophic arthritis, as certain cases are closely simulated by gout. At times the uric acid in the blood of a patient with chronic atrophic (rheumatoid) arthritis is elevated also, as it was in the patient reported here.

7. *The basal metabolic rate* should be estimated routinely.

8. *The history and physical examination* should be reviewed to evaluate contributing factors. The constitutional make-up of the patient often aids in determining the type of arthritis in borderline cases. The atrophic form occurs most often in the ptotic, asthenic, anemic patient, while the hypertrophic form is seen usually in the florid, obese, and sthenic person. There may be a long history of some debilitating disease. Nervous and physical exhaustion, such as a trying school session for a teacher, may be a most important factor in precipitating the disease, especially the atrophic form. Physical overactivity

was 20 mm. The blood count showed 4,630,000 red cells, 84 per cent hemoglobin and a color index of 0.90. A gastric analysis showed 15 degrees free acid and 36 degrees total acid. Roentgenograms of the hand and of the colon showed no abnormality. Symptomatically, she was entirely well. She was seen again one year after the first admission, and had remained well.

Comment.—The important points in the study of a patient with chronic arthritis are:

1. *A Thorough Search for a Focus of Infection.*— This patient presented the classic clinical picture of chronic atrophic (rheumatoid) arthritis in which the primary change is a proliferation of soft tissues. The common sites for focal infection are the tonsils, sinuses, dental areas and the genital organs. Any tonsil tissue is a possible source of infection, regardless of local evidence of infection. The sinuses should be thoroughly investigated and roentgenograms should be made, if indicated. Complete dental radiographs should be taken, regardless of pulpless teeth or even an edentulous mouth, since infection remains frequently after the removal of teeth and infection may be found around vital and seemingly normal teeth. The prostate in the male should be examined by palpation and the prostatic secretion obtained for microscopical study. A visual inspection of the cervix and a bimanual examination of the adnexa in the female should be a matter of routine.

2. *Radiographs of a typical joint* should be taken to aid in determining the type of disease and the extent of joint involvement, bone decalcification or hypertrophy.

3. *The sedimentation rate of the corpuscles* should always be determined. This procedure is most valuable in differentiating the two types of arthritis and helps greatly in determining the degree of activity in the atrophic type of the disease. The sedimentation rate seldom is increased in uncomplicated chronic hypertrophic arthritis and is always above normal in active atrophic (rheumatoid) arthritis. With improvement in chronic atrophic (rheumatoid) arthritis, the sedimentation rate decreases, so it is an excellent index of the patient's progress.

4. *A complete study of the gastro-intestinal tract* is most

Treatment.—Treatment was instituted as follows on the basis of the clinical and laboratory study:

1. *Rest in Bed.*—Most patients with chronic atrophic arthritis have the idea, often obtained from their physicians, that to remain in bed will only make the joints stiffer. Nothing is further from the truth. Rest in bed is the primary indication in treatment. It is apparent that the joints should not be allowed to stiffen from lack of use while the patient is in bed. The patient should have joint use while having body rest. It is most important also to have rest in bed for a sufficiently long time. This usually means a period of weeks, just as in pulmonary tuberculosis. This patient was kept at rest in bed without bathroom privileges for two months. During this time by voluntary use and manipulation by a physiotherapist the joints became much more mobile instead of stiffer.

2. *Diet.*—I am sure that a proper diet is a most important link in treatment. We have been using almost routinely a diet in which there is very little carbohydrate and a rather low caloric content. Abundant vitamins and proteins are provided. Patients usually lose weight on this regimen, which is desirable. In overweight patients, it is often best to give only fruit juices for five days after admission and then to begin the diet indicated. This diet should not be kept up indefinitely as a rule. After recovery is under way, many patients do better with larger amounts of carbohydrate. A balanced diet should be continued indefinitely, however.

3. *Added Vitamins.*—There is much evidence to show that a lack of vitamin B is a factor in the causation or continuation of the joint disease. Vitamin B should be provided as wheat germ or yeast. Embo and Bemax are purified wheat germ preparations and are very satisfactory. Vegex is a yeast extract which is an excellent source of this vitamin. Vitamins A and D, also should be given in the form of cod liver oil or halibut liver oil.

4. *Physiotherapy.*—This is almost a necessary adjunct in treatment but should be general as well as local. For local treatment diathermy, massage and manipulation of affected joints

often precipitates the symptoms in a previously silent chronic hypertrophic arthritis. All such factors must be recorded on the patient's balance sheet.

RESULTS OF CLINICAL AND LABORATORY STUDY

The patient described had a low-grade fever without leukocytosis (Fig. 167). No focal infection could be found after careful search. Fever does not necessarily indicate infection. Patients with toxemia due to other than bacterial causes often have fever. During the active stage of pernicious anemia there is almost always some fever. Malignancy is frequently the cause of fever, especially when the liver is involved. Numerous other clinical examples of nonbacterial fever might be cited.

The sedimentation rate of the red corpuscles was 78 mm. in one hour (normal 5 to 15). In the absence of some contributing cause, this rate indicates an exceedingly active form of arthritis.

The blood study showed a typical hypochromic anemia. The red cell count was over 5,000,000 but the hemoglobin was only 71 per cent, giving a color index of 0.66. This finding practically always indicates an iron deficiency as the cause of the anemia. The uric acid of the blood was 5.1 mg. There is no apparent explanation for this finding.

A radiograph of the hand to show any possible joint or bone changes showed only decalcification of bone.

The roentgenographic study of the gastro-intestinal tract had shown a poorly functioning gallbladder with the dye test. This disturbance in function, I think, was due to the general condition of the patient and not to local disease of the gallbladder. The most significant finding was an immense atonic colon. This was interpreted as due to a loss in tone, secondary to the general condition, or to some dietary deficiency such as lack of vitamin B. The basal metabolic rate was minus 14 per cent. Gastric analysis showed a very low acidity: The free acid was 3 degrees and the total acid 8 degrees.

No contributing factor in the patient's environment, past history or physical examination could be elicited.

little difference what vaccine is used, so far as one can judge from the published reports.

It seems to me increasingly evident that the effect of vaccines is largely nonspecific. With this in mind I have depended largely on the use of stock typhoid-paratyphoid vaccine for its nonspecific effect. We inject intravenously 25 million bacteria at the first treatment, give the succeeding injection after twenty-four hours of normal temperature, and double the preceding dose each time. The temperature reaction from the first dose usually lasts longer than twenty-four hours, so seventy-two hours elapse between the first and second dose. The succeeding reactions are less prolonged so that the injections after the first can be given every second day. Three to ten injections are given, as a rule. This patient had five injections. Note the return to normal of the temperature curve after the treatment (Fig. 167).

8. *Removal of Foci of Infection.*—All demonstrable foci of infection should be removed before treatment is complete. None was found in this particular patient. Much clinical judgment is required in deciding just when focal infection should be removed. Often a patient is made worse by the extraction of a tooth or a tonsillectomy. It is far better to remove infection after the patient is on the upgrade, so we seldom suggest an operation of any kind for patients with a very active, progressive and serious chronic arthritis, unless there is very evident focal disease. In the milder form and early in the disease, operation usually is not contraindicated. Early removal should always be the practice, if possible.

Results of Treatment.—This patient has had an excellent result from the treatment. The symptomatic relief is complete, and the joint swelling has disappeared entirely. The motion of some joints, especially of the wrists, is limited, due to permanent changes which cannot be undone. The psoriasis has disappeared entirely and the nails have returned to normal. The patient has returned to her normal activities.

We see all too frequently patients who are symptomatically improved but who show on special examination that the funda-

are used. The paraffin bath is especially valuable but can be used only for hands and feet.

Physiotherapy is employed to loosen up tissues in and around the joints to improve the local circulation. Still more important, however, is its general tonic effect on the general circulation and metabolism. For the general effect, radiation with an ultraviolet lamp or sun baths, when these are possible, are always used. Breathing and postural exercises and abdominal massage help much to add tone to the thoracic and abdominal circulation and can always be employed.

5. *Medication*.—This is a small part of the treatment. Many patients have a hypochromic anemia which responds almost specifically to large doses of iron (60 to 80 grains of Bland's pills or iron ammonium citrate every day). Arsenic is probably the one most valuable drug in the treatment of chronic atrophic arthritis. I prefer to use it in the form of neoarsphenamine. A dose (0.3 to 0.45 Gm.) is given twice a week for about ten injections. Thyroid extract may be tried if the metabolic rate is low. It usually is well tolerated. Dilute hydrochloric acid should be given if the acid is low or absent in the gastric secretion.

6. *Control of Constipation*.—This is most important, especially at the beginning of treatment. We usually begin with castor oil for one or two doses and then employ other laxatives as indicated. In some cases, it is advantageous to use sodium phosphate in half-drachm doses after each meal.

7. *Vaccine Therapy*.—Many vaccines are offered for the treatment of chronic atrophic (rheumatoid) arthritis, each with the claim that it is specific. I see no objection to trying vaccines, provided the main reliance in treatment is not placed on them. Two different methods of administration are employed. Some workers advocate the use of exceedingly small doses, gradually increasing over a long period of time with the idea of desensitizing the patient. Others attempt to immunize with larger doses. More recently, intravenous rather than subcutaneous injection has been popular. It probably makes

SUMMARY

Many physicians seem utterly helpless when confronted with the problem of treating chronic arthritis. So often a patient has infections removed and is then told that nothing else can be done. I have tried to emphasize in describing this patient the many factors that may be contributory in causing chronic atrophic (rheumatoid) arthritis, the necessity for thorough study of such a patient and measures which may be instituted to help and often entirely to relieve the patient's active disease. With intelligent management, the viewpoint concerning the possibility of help for the patient may be changed from the all too frequent pessimism to a justifiable optimism.

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mental difficulty is unchanged. This patient returned to the hospital for a check-up one month and six months and again one year after discharge. The last examination showed a sedimentation rate of 20 mm. as contrasted with an initial rate of 78 mm. This is the best evidence of fundamental improvement. The temperature, which returned to normal after the nonspecific protein therapy, has remained normal. The hypochromic anemia has been relieved and the gastric acidity is higher. A barium enema shows, interestingly enough, a normal colon in place of the enormously dilated one found at the initial examination. Constipation is much less marked. The basal metabolic rate is higher and the blood uric acid is normal.

Prognosis.—Every clinician sees patients with arthritis recover and later again become afflicted with the disease. A person who has had active pulmonary tuberculosis, which becomes inactive on treatment, may easily have a recurrence of activity with exhaustion, exposure, intercurrent disease and other debilitating factors. The person who has chronic atrophic (rheumatoid) arthritis may well be compared to such a patient with tuberculosis. I try to explain to each person with chronic arthritis that he always is crippled in the sense that special care must be taken to prevent a recurrence of active symptoms. This means care in preventing exhaustion from overwork or nervous strain, exposure, improper diet and intercurrent infections. With care, such a patient should be able to prevent the recurrence of active joint disease.

With proper study and treatment of chronic atrophic arthritis one can be optimistic concerning the relief of symptoms and even of cure of the disease. Many patients, unfortunately, cannot afford the expense of local treatment. The results of treatment depend almost entirely on the breadth of view in respect to contributing factors and indications for treatment exercised by the physician, provided the patient is cooperative and persists in treatment for a sufficiently long time.

to advise colectomy to get rid of the intestinal stasis which he considered the cause of arthritis. Excessive and unphysiologic purging has always been one of the evils of treatment of the disease.

The gastro-intestinal tract has also received much attention through the possible rôle that diet might play in arthritis. The elimination of meat and animal protein and emphasis on fruit and vegetables by certain powerful and enthusiastic advocates has had a far-reaching effect on the general public. Generally conceded to have no scientific foundation but to be only a creed or empirical idea, this teaching is rapidly losing ground. Based on more scientific data, however, is the teaching of Pemberton² who advocates a low-carbohydrate diet. The scientific reasoning behind this view does not relate to the gastro-intestinal tract but to the frequent occurrence of a decreased glucose tolerance in these patients which is thought to be caused by an inability of the tissues to utilize sugar properly. And it is known that an increased accumulation of glucose in the general circulation seems to aggravate the arthritic condition. With the growing enthusiasm for the part that vitamin deficiency might play in all diseases the diet has naturally received attention along this line.

For many years Goldthwaite and Osgood³ have recognized the importance of proper function and elimination of the gastro-intestinal tract. A large proportion of the patients with chronic arthritis are of the visceroptotic habitus with poor posture, low vital capacity and the asthenic type of digestive disturbance. These workers approached the problem in a normal and physiologic manner of using physiotherapy, corrective exercises and other orthopedic measures to improve the well-being of the patient, with excellent results in many cases.

Many writers have called attention to the decrease or complete absence of hydrochloric acid in the gastric secretion of arthritic patients and Pemberton⁴ of Liverpool treats his patients almost exclusively with extremely large doses of dilute hydrochloric acid and a low-carbohydrate diet, emphasizing especially the correction of the deficiency of hydrochloric acid.

THE GASTRO-INTESTINAL TRACT IN CHRONIC ATROPHIC (RHEUMATOID) ARTHRITIS

CHARLES HARTSOCK

CHRONIC atrophic (rheumatoid) arthritis still remains one of the most universal and difficult problems facing the medical profession of today. Following the general trend of scientific thought, great progress has been made to impress both the practicing physician and the patient that infection is a necessary etiologic factor in chronic arthritis. This is undoubtedly true and newer research work is also beginning to throw some light on the repeated failure of the removal of simple infection to cure the disease by demonstration that allergic and chemical factors secondary to the infection must also be combated before the fire of this affliction is extinguished. A point that is frequently overlooked, however, in the treatment of this disease is the more recently recognized fact that there are other factors in addition to the infection which play a part by preparing a suitable soil for the infection or to predisposing the patient by lessening his or her resistance.

There are probably many factors such as hereditary diathesis, chemical and vitamin deficiency, fatigue, sympathetic vascular disturbances and others, all or any one of which could produce an environment within the patient suitable for the implantation of the infective agent of arthritis. My purpose here is to discuss the possible rôle of disturbances and organic changes in the intestinal tract as one of the secondary etiologic factors of the arthritic diathesis.

Constipation has been such a frequent accompanying symptom of chronic arthritis that it alone has been attributed by many, and especially by the patients themselves, as the sole cause of their trouble. Lane¹ went so far in this direction as

I have selected for analytical study the last 100 cases of typical atrophic arthritis. The patients in this group included those with arthritis of early mild degree to those with severe cases of long standing and with marked deformity. The ages ranged from eighteen to seventy-six years. The ratio of women to men was 2 to 1.

In the study of this group the dietary factor was the most difficult to evaluate. Where the patient's story was satisfactory, there was very little evidence of a deficiency except in quantity. In quite a few cases, protein had been slighted in favor of carbohydrate, but no general conclusions could be formed in respect to the dietary factor.

Symptoms were studied solely from the standpoint of digestive distress and chronic obstinate constipation for which the patient used regular laxatives or other treatment. Sixteen patients suffered with chronic dyspepsia of some type. Six had marked anorexia, 2 had chronic or frequent attacks of diarrhea, 61 had obstipation and 26 had no symptoms.

In studying the gastric secretion, a purely arbitrary division was made in the classification of those with normal acidity (30 to 60 free HCl), hyperacidity (50 plus HCl), subacidity (30 to 10 HCl) and achlorhydria (below 10). In 8 cases there was no record of gastric analysis. Three patients had hyperacidity, 19 had normal acidity, there were 47 with hypo-acidity, and in the group with achlorhydria there were 23 patients.

Roentgenographic studies revealed gastro-intestinal abnormalities. The list follows: Dilated stomach, 1; duodenal ulcer, 2; dilated duodenum, 3; ptosed colon, 4; diverticulosis, 5; ulcerative colitis, 1; inverted cecum, 1; nonfunctioning gall-bladder, 10; gallstones, 4; chronic appendicitis, 4; atonic right colon, 14; atonic whole colon, 22; redundant colon, 30; spastic left colon, 7; general visceroptosis, 2; and 22 patients showed no abnormalities. Four patients in the series did not have roentgenographic study of the gastro-intestinal tract.

Sixty-six patients showed some type of disease of the colon, 60 of them some degree of atony or redundancy. In the whole group of the 100 cases only 3 patients were entirely free of

Fletcher and Graham⁵ have approached the problem of the gastro-intestinal factor in arthritis in still a different manner. In 65 per cent of their patients there was an atonic condition of all or some part of the colon. Based on McCarrison's work of feeding animals a deficient, high-carbohydrate diet which resulted in disturbances of nutrition and a dilation of the colon, these authors came to the conclusion that general nutrition is a vital part in the etiology of arthritis and that the nutrition is lowered through deficiency of vitamins and excessive carbohydrate with characteristic gastro-intestinal changes. Therapeutically they emphasize a diet high in vitamin content, especially vitamin B, and a low-carbohydrate diet and show conclusively that with this treatment there is tendency for the colon to return to the normal with concomitant improvement in the arthritis.

These various approaches toward correcting disorders of the gastro-intestinal tract would indicate very strongly that these disorders are more than coincident and that they are related in some way to chronic arthritis.

In the Cleveland Clinic it has been realized for a long time that other factors in addition to infection dominate the situation in chronic arthritis. Roughly speaking, malnutrition, easy fatigability and chronic exhaustion form the background of the patient with chronic atrophic (rheumatoid) arthritis. Under the direction of Drs. Haden and Duncan this problem has been approached not by a single line of attack but each patient has been studied in an effort to uncover every possible exhaustive factor in addition to infection. Hematological studies, chemical estimations of various substances in the blood, investigations of the vascular and sympathetic nervous systems as well as environmental, postural and gastro-intestinal studies have been made.

The latter has been approached by a history of the patient's diet, digestive upsets and elimination. Gastric analysis, roentgenographic study of the colon routinely and of the entire gastro-intestinal tract, if possible, and under certain conditions, stool examinations and culture are done.

allow the patient to continue the diet, but if the distress continues, a smooth nonresidue diet must be substituted.

Hydrochloric acid is always given to patients with achlorhydria and usually is tolerated well and seems to be of decided benefit in improving his general health. Treatment of the less common conditions is given according to the indications.

It is of the utmost importance that the nutritional factor be improved before any further exhausting treatment be instituted, such as operative procedures, vaccine and typhoid therapy. The purpose of this paper is to emphasize that investigation and treatment must be directed toward the gastrointestinal tract, even in the absence of symptoms, in a disease which manifests itself chiefly in the joints but in which there are also constitutional factors affecting the nutrition.

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gastric symptoms, abnormal roentgenographic finding or disturbance of the gastric secretion. All the others showed marked change from normal in one or all of these ways.

The question naturally arises: Does this high percentage of abnormal findings in the gastro-intestinal tract prove that these are an etiologic factor or are these changes secondary to the disease itself?

No direct evidence can be brought forth to prove that the disturbances in the gastro-intestinal tract bear a causal relation to arthritis but certain evidence points toward this conclusion: (1) The percentage of cases in which there is some gastro-intestinal disturbance is much greater than is encountered in other exhausting diseases; (2) the gastro-intestinal symptoms and findings are just as marked in early cases and in young people as in the old, long-standing cases; and (3) in the absence of other pathologic features the arthritis has responded to treatment of the gastro-intestinal tract alone. These reasons do not prove conclusively that the digestive findings are primary but there is no question that the changes described are of pathologic significance in the nutrition of the patient. Furthermore, improvement in the general condition of the patient is *sine qua non* in the treatment of arthritis. Hence the therapeutic importance of these factors suggests that the gastro-intestinal tract should be studied in every case of chronic arthritis in order that the proper treatment may be instituted. The practical application of this is demonstrated in the case reported by Haden (p. 903).

For the treatment of the atonic colon general upbuilding measures are employed such as physiotherapy, low-carbohydrate, high-vitamin diet, with especial emphasis on vitamin B. Anticonstipation measures should be instituted to avoid the use of laxatives. Occasionally colon irrigations may be necessary. In the case of an atonic right colon with a spastic left colon, the roughage in the low-carbohydrate diet may be very distressing and have to be discontinued. Rest, heat to the abdomen and antispasmodics may give sufficient relief to

cularity of the thyroid gland constitutes a kind of arteriovenous shunt which increases the work of the heart just as would a traumatic arteriovenous aneurysm. After thyroidectomy the basal metabolic rate and blood flow decrease to within the limits of normal, and the patients, with few exceptions, regain a normal exercise tolerance.

Physical examination in patients with uncomplicated hyperthyroidism reveals constant overactivity of the heart. The heart rate is increased and remains elevated even during sleep. The apex impulse is forcible but diffuse, differing in the latter respect from the well-defined thrust of an hypertrophied heart. Percussion of the cardiac borders frequently is difficult, and one may conclude wrongly that the heart is enlarged. On auscultation the first sound at the apex is increased in intensity and snapping in quality. Systolic murmurs are frequently present and are of two types. The most common type is heard in the second or third left intercostal space adjacent to the sternum and usually is blowing in quality, although at times it may be distinctly harsh. The second type is a blowing murmur with its point of maximum intensity at the apex and probably results from dilatation of the mitral valve ring. Diastolic murmurs are not present although a rough first sound at the apex and the elevated heart rate occasionally may combine to create the impression of a presystolic rumble. None of these physical findings is to be interpreted as evidence of myocardial damage. The heart is performing an increased amount of work in order to meet the increased metabolic needs of the body. At the same time, the metabolic rate of the myocardium presumably is elevated along with that of the tissues in general,⁴ and the cost of cardiac work probably increased just as is the cost of work by skeletal muscles. These factors adequately explain the hyperactivity of the heart and the accompanying physical signs.

CARDIAC ARRHYTHMIAS AND CONGESTIVE MYOCARDIAL FAILURE IN HYPERTHYROIDISM

In certain individuals with hyperthyroidism, more important cardiovascular symptoms and signs are observed. Dis-

THE HEART IN HYPERTHYROIDISM

A. CARLTON ERNSTENE

SINCE the original description of exophthalmic goiter by Parry,¹ it has been recognized that symptoms and signs referable to the cardiovascular system occupy a prominent place in the clinical picture of hyperthyroidism. Dyspnea on exertion, tachycardia and palpitation are present to a certain degree in practically all thyrotoxic patients. In the absence of signs of congestive myocardial failure, however, these symptoms are not to be regarded as evidence of cardiac damage or of myocardial insufficiency but rather as direct manifestations of the hyperthyroid state. In order to meet the increased metabolic needs in hyperthyroidism, the tissues of the body must be supplied with an increased amount of blood per minute. This is accomplished principally by changes in pulse rate, minute volume output of the heart and velocity of blood flow, all of which are increased roughly in proportion to the elevated basal metabolic rate.² As a result, blood flow in hyperthyroid patients at rest is equivalent to the flow in normal persons during moderate exercise, and to this extent the resting circulatory reserve is encroached on by thyrotoxic patients. Plummer and Boothby³ observed that the cost of work is increased in hyperthyroidism. A given amount of work is accompanied by an abnormal rise in the metabolic rate which necessitates a corresponding abnormal increase in blood flow and pulmonary ventilation. In addition, the vital capacity usually is diminished in patients with hyperthyroidism and the degree to which pulmonary ventilation can be increased during exercise without the production of dyspnea therefore is reduced. These factors account for the fact that relatively little exercise may produce symptoms in thyrotoxic patients equivalent in severity to those observed in normal subjects only after severe and prolonged exertion. It has been suggested also that the increased vas-

of all patients with hyperthyroidism, but in more than three-fourths of the cases in which it does develop, auricular fibrillation has been present for some time. When congestive failure occurs in the presence of normal cardiac rhythm, the patient, as a rule, is over forty years of age and some complicating factor, usually hypertension or arteriosclerosis, less commonly valvular heart disease, is almost invariably present. Myocardial failure with normal cardiac rhythm is extremely rare in young hyperthyroid subjects even though valvular heart disease is present. The following case illustrates the occurrence of auricular fibrillation and congestive failure in a patient with hyperthyroidism, arteriosclerosis and arterial hypertension.

Case I.—The patient, a married woman, sixty-four years of age, had complained of nervousness, fatigability, palpitation, and dyspnea on exertion for four years and during this time had lost approximately 90 pounds. The thyroid gland had been enlarged since the patient was twelve years of age but there had been no recent increase in its size. During the two months before admission to the hospital, the dyspnea had increased progressively in severity and there had been a frequent, moderately productive cough. Edema of the legs had been present for the last three days of this period.

Physical examination revealed a hyperactive, very poorly nourished patient with moderately severe orthopnea. There was slight exophthalmos and a definite lid lag. The skin was warm and moist, and the lips were faintly cyanotic. The thyroid gland was enlarged to approximately three times its normal size and contained a nodule 3 cm. in diameter in the right lobe. The jugular veins were engorged to the angle of the jaw with the patient elevated in bed at an angle of 60 degrees. The apex impulse of the heart was forcible but diffuse. Relative cardiac dullness extended 11 cm. to the left of the midsternal line. The cardiac rhythm was absolutely irregular with a ventricular rate of approximately 150 beats per minute. The first sound at the apex was increased in intensity, and a blowing systolic murmur

turbances of heart rhythm occur in 10 or 15 per cent of all hyperthyroid patients. The most common abnormal rhythm is auricular fibrillation although auricular flutter, paroxysmal auricular tachycardia and auricular premature beats are observed at times. All of these arrhythmias are to be regarded as having the same clinical significance. Auricular fibrillation may be present continually or may occur in paroxysms of long or short duration. Occasionally, also, in patients in whom the cardiac rhythm has been regular during the entire course of hyperthyroidism, auricular fibrillation develops within the first two days following thyroidectomy and then usually disappears during the next twenty-four or forty-eight hours.

The exact mechanism by which auricular fibrillation is produced during the course of hyperthyroidism or in the early postoperative period is not known. It is a well-established clinical fact, however, that the arrhythmia seldom occurs in patients who have normal hearts. It is uncommon in patients less than forty years of age, and in practically all hyperthyroid individuals above this age in whom the arrhythmia does occur, hypertension is present or the possibility of changes in the coronary arteries cannot be excluded. The conclusion seems warranted, therefore, that the presence of auricular fibrillation in thyrotoxic patients should lead one to search thoroughly for evidence of some earlier change in the myocardium which may have predisposed to the development of the abnormal rhythm.

One of the most important features of auricular fibrillation in hyperthyroidism is that the ventricular rate usually cannot be controlled satisfactorily until the hyperthyroidism has been treated adequately. As long as the basal metabolic rate remains elevated, it is seldom possible to reduce the ventricular rate permanently to below 100 beats per minute by the use of digitalis alone. Furthermore, if the irregularity is present for a considerable length of time in untreated thyrotoxicosis, the myocardial reserve may be exhausted and signs of congestive heart failure, such as cough, increased venous pressure, engorgement of the liver, dependent edema and orthopnea may develop. Myocardial failure occurs in only a relatively small proportion

of all patients with hyperthyroidism, but in more than three-fourths of the cases in which it does develop, auricular fibrillation has been present for some time. When congestive failure occurs in the presence of normal cardiac rhythm, the patient, as a rule, is over forty years of age and some complicating factor, usually hypertension or arteriosclerosis, less commonly valvular heart disease, is almost invariably present. Myocardial failure with normal cardiac rhythm is extremely rare in young hyperthyroid subjects even though valvular heart disease is present. The following case illustrates the occurrence of auricular fibrillation and congestive failure in a patient with hyperthyroidism, arteriosclerosis and arterial hypertension.

Case I.—The patient, a married woman, sixty-four years of age, had complained of nervousness, fatigability, palpitation, and dyspnea on exertion for four years and during this time had lost approximately 90 pounds. The thyroid gland had been enlarged since the patient was twelve years of age but there had been no recent increase in its size. During the two months before admission to the hospital, the dyspnea had increased progressively in severity and there had been a frequent, moderately productive cough. Edema of the legs had been present for the last three days of this period.

Physical examination revealed a hyperactive, very poorly nourished patient with moderately severe orthopnea. There was slight exophthalmos and a definite lid lag. The skin was warm and moist, and the lips were faintly cyanotic. The thyroid gland was enlarged to approximately three times its normal size and contained a nodule 3 cm. in diameter in the right lobe. The jugular veins were engorged to the angle of the jaw with the patient elevated in bed at an angle of 60 degrees. The apex impulse of the heart was forcible but diffuse. Relative cardiac dullness extended 11 cm. to the left of the midsternal line. The cardiac rhythm was absolutely irregular with a ventricular rate of approximately 150 beats per minute. The first sound at the apex was increased in intensity, and a blowing systolic murmur

was present. The aortic second sound was moderately accentuated, and a rough systolic murmur was heard in the second and third left interspaces adjacent to the sternum. The blood pressure was 180 systolic and 90 diastolic. The percussion note was impaired over the base of both lungs posteriorly, more extensively on the right than on the left, and numerous medium moist râles were heard. The liver extended 5 cm. below the costal margin and was very tender. There was moderate pitting edema of the lower extremities and over the lower back.

The basal metabolic rate was plus 39 per cent. Roentgenological examination of the thorax showed an enlarged heart with evidence of extensive congestion in both lungs. An electrocardiogram revealed auricular fibrillation and left axis deviation.

With rest in bed, limitation of fluids to 1500 cc. daily, and the administration of digitalis, Lugol's solution and sedatives, the signs and symptoms of congestive myocardial failure rapidly disappeared, the ventricular rate decreased to approximately 80 beats per minute and the basal metabolic rate dropped to plus 19 per cent. Subtotal thyroidectomy was performed on the thirteenth day after admission to the hospital. The subsequent course was uneventful, and the patient was discharged on the ninth day after operation. Auricular fibrillation was still present, but there were no signs of congestive failure.

At the time of subsequent examination two weeks later, the cardiac rhythm was regular and the rate 84 per minute. The blood pressure was 170 systolic, 104 diastolic. The patient has been carrying on moderate daily activities without symptoms of myocardial insufficiency, and had gained 9 pounds.

In approximately one half of all patients with hyperthyroidism and auricular fibrillation, the cardiac rhythm spontaneously becomes regular during the early part of convalescence from thyroidectomy; and in a majority of the remaining patients, normal sinus rhythm can be restored by the oral administration of quinidine sulphate. Auricular fibrillation subsequently

recurs in only a few cases, and hence it appears that the myocardial changes which favor the development of the abnormal rhythm during hyperthyroidism usually are of limited clinical significance in the absence of hyperthyroidism.

The reversion to regular rhythm, as a rule, is uneventful, both in patients in whom it occurs spontaneously and in those in whom it follows the administration of quinidine. Patients with mitral stenosis and auricular fibrillation constitute an exception to the general rule. In these patients the arrhythmia fortunately tends to persist after thyroidectomy, and quinidine therapy is seldom employed because reversion to normal rhythm is attended by a definite risk of serious accident due to embolism. The emboli arise from thrombi situated usually in the auricles; small particles of thrombotic material are broken off when normal auricular action is restored and may lodge in any part of the vascular tree. Serious symptoms, when they arise, usually are due to embolic occlusion of a cerebral vessel. In the following case, sudden death occurred a few hours after spontaneous reestablishment of normal sinus rhythm in a patient with mitral stenosis.

Case II.—The patient, a white, single female, sixty-three years of age, complained chiefly of nervousness, weakness, dyspnea on exertion, palpitation and loss of weight, which had persisted for one year. The past medical history was irrelevant except that there had been frequent attacks of tonsillitis during childhood and adolescence. Physical examination revealed an undernourished, hyperkinetic woman with moderate flushing of the skin of the face and neck and a rapid, fine digital tremor. There was no exophthalmos but a definite staring expression was present. The isthmus of the thyroid gland was palpable and seemed to extend down behind the sternum. The area of relative cardiac dulness extended 10.5 cm. to the left of the mid-sternal line in the fifth interspace. Auricular fibrillation was present with a ventricular rate of 120 beats per minute and a moderate radial pulse deficit. The first sound at the apex was loud and snapping in quality, and systolic and diastolic apical murmurs were present. The blood pressure was 146 systolic,

was present. The aortic second sound was moderately accentuated, and a rough systolic murmur was heard in the second and third left interspaces adjacent to the sternum. The blood pressure was 180 systolic and 90 diastolic. The percussion note was impaired over the base of both lungs posteriorly, more extensively on the right than on the left, and numerous medium moist râles were heard. The liver extended 5 cm. below the costal margin and was very tender. There was moderate pitting edema of the lower extremities and over the lower back.

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to the onset of the present illness suggested that the auricular fibrillation did not antedate the onset of hyperthyroidism. Spontaneous establishment of normal heart rhythm after operation therefore might have been anticipated, but on clinical grounds the likelihood of such an occurrence could not be considered great. Although the brain was not examined, the manner of death and the absence of evidences of embolism in the pulmonary or coronary vessels seems to establish the diagnosis of cerebral embolism. Since embolic phenomena are very rarely observed following uncomplicated thyroidectomy while they occur not infrequently soon after the change from auricular fibrillation to normal sinus rhythm in patients with mitral stenosis, the source of the embolus in this case probably was the thrombus in the left auricle.

HYPERTHYROIDISM MASKED AS HEART DISEASE

Levine and Sturgis⁵ and others have directed attention to a group of patients with hyperthyroidism in whom exophthalmos and enlargement of the thyroid gland are absent and symptoms and signs referable to the cardiovascular system dominate the clinical picture. The presence of so-called "latent hyperthyroidism" usually is overlooked for some time, and the patient is treated, with little or no success, as if he had primary cardiovascular disease. A careful history and physical examination, however, reveal certain features which should suggest the possibility of thyrotoxicosis. Nervousness, tremor, diminished tolerance to heat and weight loss in spite of a satisfactory appetite usually are present at least to a slight degree. Increased warmth and moisture of the skin, a peculiar flushed appearance of the face and neck and the presence of a hyperactive heart with a snapping first sound are helpful diagnostic features. Of particular importance is the occurrence of auricular fibrillation, either in paroxysms of variable duration or in its established form. Frequently it is this that first suggests the true nature of the illness. Several observers have expressed the opinion that the presence of auricular fibrillation always should lead one to consider the possibility of hyperthyroidism

and 80 diastolic. There were no signs of congestive myocardial failure.

Roentgenological examination of the thorax revealed a large substernal thyroid gland which contained several areas of calcification and extended below the level of the arch of the aorta. The size of the cardiac shadow was moderately increased with prominence of the left upper border. There was evidence of considerable fibrosis throughout the lower part of both lungs. The electrocardiogram revealed auricular fibrillation and inversion of the T wave in lead III. The basal metabolic rate was plus 35 per cent.

The following diagnosis was made: Hyperthyroidism, substernal goiter, rheumatic heart disease, enlargement of the heart, mitral stenosis and insufficiency, and auricular fibrillation.

With rest in bed, Lugol's solution, digitalis and liberal amounts of fluids, the ventricular rate gradually decreased to approximately 80 beats per minute and the basal metabolic rate dropped to plus 24 per cent. Subtotal thyroidectomy was performed on the tenth day after admission to the hospital. The cardiac rhythm became regular early on the morning of the first day after operation, and although the patient was somewhat restless, her general condition appeared to be satisfactory. Five hours later, however, and approximately twenty-six hours after operation, she died suddenly.

Necropsy Findings.—The heart weighed 420 Gm. Both auricles contained organized thrombotic material. The mitral valve leaflets were greatly thickened and contracted, and the lumen of the valve was reduced to a small curved slit. The aortic valve leaflets were slightly thickened but not otherwise abnormal. The coronary vessels were patent throughout. The lower lobes of the lungs contained a moderately increased amount of moisture, but neither on gross nor microscopical examination were areas of infarction or atelectasis discovered. The abdominal and pelvic viscera were normal. Permission to examine the brain was not obtained.

Comment.—The absence of cardiovascular symptoms prior

and left axis deviation. The basal metabolic rate was plus 52 per cent.

With rest in bed and the administration of digitalis, Lugol's solution and sedatives, the ventricular rate decreased gradually to 90 beats per minute and the basal metabolic rate fell to plus 34 per cent. Subtotal thyroidectomy was performed on the twelfth day after admission to the hospital, and the patient was discharged on the ninth day after operation. Three weeks later auricular fibrillation still was present. The ventricular rate had been maintained at approximately 80 beats per minute with daily doses of digitalis. The patient had gained 14 pounds and was able to carry on moderate activities without respiratory discomfort.

ANGINA PECTORIS IN HYPERTHYROIDISM

An occasional patient with hyperthyroidism experiences attacks of angina pectoris. The first seizure of anginal pain usually occurs after the onset of active hyperthyroidism, although at times a history of earlier attacks is obtained. In the latter group of patients it is observed that after the onset of hyperthyroidism the pain is brought on by less exertion than formerly. Hyperthyroidism *per se* probably is not capable of causing angina pectoris; and when patients with thyrotoxicosis experience attacks of anginal pain, the existence of some organic change in the heart, usually sclerosis of the coronary arteries, must be assumed. In other words, the presence of hyperthyroidism seems to bear the same relation to the production of anginal pain as does exertion in subjects with a normal metabolic rate. As stated previously, the heart is forced to perform an increased amount of work in patients with hyperthyroidism even with the patient at rest, while any exertion necessitates a much greater than normal expenditure of energy. It is probable, therefore, that relatively slight pathologic changes in the heart may at times be sufficient for the production of angina pectoris during thyrotoxicosis.

The degree of activity necessary to produce an attack varies in different subjects from slight to moderately strenuous,

even though obvious organic heart disease also is present. The following case report is illustrative of hyperthyroidism masked as heart disease.

Case III.—The patient, a white married woman, aged fifty-four, was admitted to the hospital because for one year she had complained of dyspnea on exertion, palpitation and fatigability. The past medical history was irrelevant except that the existence of an elevated blood pressure had been known for two years. A frequent, unproductive cough had been present for several weeks before the patient came to the hospital, and for the same length of time there had been slight edema of the ankles toward the end of the day. The administration of digitalis and a period of rest in bed had not resulted in improvement in the symptoms. The patient denied nervousness, abnormal perspiration and intolerance to heat. There had been a gain of 5 pounds in weight during the year.

On physical examination the patient was alert but not hyperactive. There was no evidence of respiratory discomfort while at rest. There was no exophthalmos. The skin was not remarkable except for slightly increased moisture. The isthmus of the thyroid gland was palpable but did not seem enlarged. A fine digital tremor was present. There was no evidence of increased pressure in the peripheral veins. The brachial and radial arteries were moderately thickened. The blood pressure was 190 systolic, and 100 diastolic. The area of relative cardiac dulness extended 13 cm. to the left of the midsternal line. The first sound at the apex was forceful, and at the base both second sounds were increased in intensity. The rhythm was absolutely irregular with a ventricular rate of approximately 160 beats per minute. No murmurs were audible. A few medium moist râles were heard at the base of both lungs posteriorly. The liver was not enlarged or tender but there was slight pitting edema over the ankles and lower legs.

Roentgenological examination of the thorax showed an enlarged heart and increased density throughout the lower part of both lung fields. An electrocardiogram revealed auricular fibrillation with a ventricular rate of 154 to 176 beats per minute

thickened. The blood pressure was 136 systolic, and 74 diastolic. The remainder of the examination was essentially negative. An electrocardiographic tracing revealed no abnormalities. The basal metabolic rate was plus 54 per cent.

Preoperative management consisted of rest in bed and the administration of Lugol's solution for ten days. Subtotal thyroidectomy was then performed. The postoperative course was uneventful, and the patient was discharged on the twelfth day after operation. There had been no recurrence of anginal pain four months later, at which time the basal metabolic rate was plus 3 per cent.

PATHOLOGIC CHANGES IN THE HEART IN HYPERTHYROIDISM

Because of the frequent occurrence of symptoms referable to the cardiovascular system in patients with hyperthyroidism, numerous studies have been made to determine whether thyrotoxicosis commonly produces gross or microscopical changes in the heart. Early studies were confined to individual cases or to small series of cases and frequently were of limited value because proper importance was not attached to the possible effect of factors other than hyperthyroidism. In recent years, however, the problem has been carefully studied on a sufficiently broad scale to allow of reliable conclusions.^{6, 7, 8, 9, 10, 11} There is now quite general agreement that hyperthyroidism by itself can cause slight or even moderate dilatation and hypertrophy of the heart, but usually the enlargement is not of sufficient degree to be detected by physical examination alone. Roentgenological examination is of considerable assistance, and may show prominence of the pulmonary arc in addition to slight cardiac enlargement. The results of necropsy studies indicate that after excluding those cases in which a possible cause of cardiac hypertrophy other than hyperthyroidism is present, a slight increase in the weight of the heart is observed in approximately one half of all patients dying of thyrotoxicosis or after thyroidectomy. Usually the increase amounts to less than 10 per cent of the calculated normal heart weight. Histologic studies have failed to demon-

depending probably upon the degree of pathologic change present in the heart and upon the height of the metabolic rate. Mild excitement or a slight emotional upset may at times precipitate the pain while the patient is at rest. Individuals who have experienced anginal attacks during hyperthyroidism frequently remain completely free from pain for a considerable period after thyroidectomy, and an occasional patient appears to be permanently relieved. In many instances, however, attacks of pain recur after a variable period, due apparently to progression of the underlying pathologic process in the heart.

Case IV.—The patient, a man, aged fifty-four, was admitted to the hospital because of nervousness, tremor, hyperhidrosis, loss of weight, subjective tachycardia and slight dyspnea on exertion which had been present for nine months. While out hunting, one month after the onset of the present illness, he experienced his first attack of sudden severe pain in the upper retrosternal region. The pain radiated to the left side of the neck and down the left arm and was of such severity as to force him to sit down. Rest resulted in prompt relief but the pain recurred four times before he reached his home a mile away. Following this experience he had experienced anginal pain on any exertion of moderate severity and at times as the result of excitement. The frequency of the attacks progressively increased, and the degree of exertion necessary for their production diminished. During the month before coming to the hospital there had been ten or twelve attacks almost every day. Rest and nitroglycerin always relieved the pain promptly.

Physical examination revealed a slender, hyperkinetic male with moist, warm skin, flushed face and neck, and slight exophthalmos. There was moderate diffuse enlargement of the thyroid gland with an easily detectable thrill and bruit. A marked digital tremor was present. The area of relative cardiac dulness was not enlarged, and the heart rhythm was regular with a rate of 116 beats per minute. The first sound at the apex was increased in intensity and snapping in quality. A harsh systolic murmur was heard in the left second intercostal space. The radial and brachial arteries were not appreciably

measures are seldom needed. Occasionally it may be necessary to employ a diuretic such as salyrgan or hypertonic glucose solution intravenously. As a general rule, the patient can be prepared for operation in ten to fourteen days.

When auricular fibrillation persists for more than seven to ten days following subtotal thyroidectomy, quinidine sulphate may be administered by mouth in an attempt to reestablish normal cardiac rhythm, provided evidence of valvular heart disease is not present. The drug may be given in a number of ways. It has been our practice to administer 0.2 Gm. (3 grains) as a test dose and to follow this by two doses of the same amount at intervals of three hours. On each subsequent day, each of the three doses is increased 0.1 Gm. This is continued until the rhythm becomes regular or toxic symptoms appear. The maximum amount of the drug administered is 1 Gm. in each of the three doses; and if this amount fails to cause reversion to normal rhythm, the drug is discontinued.

The development of auricular fibrillation during the first day or so following operation requires no special treatment in most instances. Occasionally the development of severe dyspnea and other evidences of myocardial failure may necessitate rapid digitalization. Normal sinus rhythm usually is restored spontaneously within forty-eight hours.

As previously stated, patients who have had auricular fibrillation, congestive myocardial failure or angina pectoris during the period of hyperthyroidism usually experience complete or practically complete relief from cardiovascular symptoms following thyroidectomy. After leaving the hospital, no special therapeutic measures are necessary except that persistence of auricular fibrillation may require regular administration of digitalis. It is to be remembered, however, that hyperthyroidism is very rarely, if ever, the sole cause of the cardiovascular complications of the disease. All patients, therefore, should be observed at regular intervals because of the possibility of gradual progression of the underlying pathologic process.

strate the presence of characteristic changes in the myocardium. The cardiac manifestations of hyperthyroidism, therefore, can hardly be attributed to structural changes in the heart.

MANAGEMENT OF THE HEART IN HYPERTHYROIDISM

Thyroidectomy after a period of preoperative treatment is the essential measure in the management of both uncomplicated hyperthyroidism and hyperthyroidism in patients presenting evidence of organic heart disease. The presence of cardiac arrhythmia, congestive myocardial failure or angina pectoris is not to be regarded as contraindicating surgical treatment. In active thyrotoxicosis, unaided medical management of these conditions gives unsatisfactory end-results even though a period of temporary improvement may be obtained. Control of the hyperthyroidism by thyroidectomy reduces the metabolic rate, including the metabolic rate of the myocardium, to within the limits of normal and diminishes the load upon the heart. These changes usually result in complete or practically complete relief from all signs and symptoms referable to the cardiovascular system.

Careful preparative treatment of the thyrotoxic patient with heart disease is of fundamental importance. As in persons with uncomplicated hyperthyroidism, this treatment consists of absolute rest in bed and the administration of a high-calorie diet, Lugol's solution and sedatives. Large amounts of fluids are given except in the presence of myocardial failure. These measures alone frequently result in complete relief from all cardiovascular symptoms and in disappearance of the signs of congestive failure. Digitalis is administered only to patients with auricular fibrillation or myocardial failure. If, for any reason, Lugol's solution is withheld while digitalis is administered, the latter drug frequently produces but a limited response. When both Lugol's solution and digitalis are given, however, signs of congestion in the peripheral and pulmonary circulation usually disappear rapidly and the ventricular rate in patients with auricular fibrillation generally can be reduced to between 80 and 90 beats per minute. Additional therapeutic

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Pathologic studies show that postencephalitic states result, in a large measure, from cellular changes in the gray matter of the diencephalon and the posterior portion of the telencephalon. The symptoms are produced by degeneration or inhibition in the striatal or parastriatal systems and the inflammation may even remove the inhibitory impulses coming from the cerebral cortex. The vegetative centers of the midbrain are affected in a like manner. It is evident that patients who have suffered these changes may manifest autonomic nervous disturbances which are readily confused with those present in hyperthyroidism.

In the majority of the doubtful cases in which the history and clinical findings gave insufficient evidence to establish a definite diagnosis either of hyperthyroidism or of a postencephalitic syndrome, the basal metabolic reading and therapeutic iodine test were sufficient to clarify the problem. However, the hyperthyroidism secondary to thyroiditis in Case II was only proved to be correctly diagnosed by a second therapeutic test, subtotal thyroidectomy. If reliance could be placed on metabolic readings as really basal, the problem would be simplified. However, many of the patients have had iodine within a short time before the examination, or if not, they may have a parkinsonian tremor sufficient to invalidate the metabolic study. Experience has shown that both the metabolic and iodine tests can be unreliable. Therefore the problem must be considered as a whole, with a careful evaluation of all signs and symptoms. In order to summarize important evidence in this particular problem, some of the significant data for consideration are listed on page 941.

This comparative list is by no means conclusive, but includes the factors which assist in making the differential diagnosis between hyperthyroidism and encephalitic syndromes. The symptoms, signs or laboratory tests may vary in individual cases, none more so, probably, than the basal metabolic rate. In patients suffering from the post-Parkinson syndrome, the actual basal rate is normal or low. A survey of twelve uncomplicated cases of Parkinson's syndrome, selected at random,

THE DIFFERENTIAL DIAGNOSIS BETWEEN HYPERTHYROIDISM AND POSTENCEPHALITIC SYNDROMES

JOHN TUCKER

THE differential diagnosis between hyperthyroidism and subacute encephalitis or chronic encephalitic syndromes presents a difficult clinical problem. If the symptoms, in either case, are atypical in their manifestation the difficulty is even more apparent. Both diseases are characterized by changes in the psychic state of the patient as well as disturbances in the motor and vegetative nervous systems. It is well known that these symptoms may be caused by definite disease of the brain or by brain effects secondary to endocrine disturbances. Some of the older clinicians, among whom are Dieulafoy, Trousseau and Sée, were so keenly aware of these nervous influences that they placed the etiologic pathology of Basedow's disease in the brain stem. It was felt by Dieulafoy¹ that the tachycardia of hyperthyroidism was the result of paralysis of the vagus nuclei and by Trousseau and Sée that the disease "is a neurosis of bulbar origin." Today it is realized that the nervous symptoms of Basedow's disease accompany or are the result of hypermetabolism and that the stimulus comes either directly or indirectly from the thyroid gland. However, at times the picture is so confusing that special diagnostic measures must be resorted to before disease of the central nervous system can be entirely excluded.

Von Economo² has divided the encephalitic states into three main divisions: (*a*) The somnolent—ophthalmoplegic form, (*b*) the hyperkinetic form and (*c*) the amyostatic akinetic form. As will appear in our case reports, the diagnostic difficulties arise in differentiating types (*b*) and (*c*) from cases of atypical hyperthyroidism.

realize that such a problem can exist. Likewise it is much better to make the diagnosis before rather than after thyroidectomy.

Case I. Postencephalitic Parkinsonism.—The patient, aged thirty-three, was examined at the clinic on January 2, 1931. Her major complaints were marked nervousness, tremor, weakness and dizziness.

Her *present illness* dated from an attack of influenza in 1918 when she had experienced diplopia, but had had no period of excessive somnolence. The patient never had been strong after this illness. About twelve years before admission she had had nervous spells, characterized by disturbances in memory and concentration, and more or less constant coarse tremor of the hands and a muscular incoordination which caused her to drop objects from the hands. Within the next few years she became more and more tired and developed dyspnea on exertion. Palpitation increased by exertion and also became troublesome. When she had developed some difficulty in swallowing about eight years before, her physician had discovered a goiter. During the subsequent years the nervousness and palpitation continued to be troublesome. She became especially alarmed by a recent failure in appetite and a weight loss of 7 pounds. Some two weeks before admission, her basal metabolic rate had been reported plus 27 per cent. However, a course of treatment with Lugol's solution failed to ameliorate her symptoms.

There were no significant past illnesses excepting the attack of influenza in 1918. The family history was irrelevant.

The *physical examination* showed that the patient was quite emaciated and rather pale. She weighed 91 pounds and her height was 64 inches. She manifested a coarse tremor of the upper and lower extremities which was increased by emotional excitement. Her face was expressionless with the characteristics of a mild parkinsonian mask. The eyes gave an impression of staring with prominent eyeballs and widened interpalpebral spaces. The thyroid was diffusely enlarged (grade I) with an adenoma in the left lobe. The heart was normal in size, the beat was forceful and the rate 90. The blood pressure was normal.

	Encephalitis.	Hyperthyroidism.
1. History.....	Previous attack of influenza.	Constitution, psychic trauma, infections.
2. Facies.....	Masklike, oily, jaw drop.	Animated, flushed, facial weakness late in hyperthyroidism (such as case II).
3. Eyes.....	Staring expression. Paresis of internal or external ocular muscles.	Exophthalmos =.
4. Thyroid.....	Simple goiter, adenomata.	= Hyperplastic goiter—palpable or substernal.
5. Tremor.....	Coarse—increased by emotional reactions.	Fine, rhythmic, sustained.
6. Pulse.....	Rapid—may be arrhythmic.	Rapid =, rhythmic auricular fibrillation.
7. Skin.....	Oily, greasy.	Flushed, soft moist texture, wet palms and feet.
8. Muscles.....	May be hypertonic and resistant to passive motion.	Normal weakness of legs.
9. Gait.....	Propulsive with lack of concomitant arm movement =.	Normal but readily fatigued.
10. Reflexes.....	Sluggish.	Normal or hyperactive.
11. Emotions.....	Usually lethargic. Unstable in hyperkinetic types.	Stimulated.
12. Spinal fluid.....	Normal or abnormal.	Normal.
13. B. M. R.....	Normal, low or high (when tremor is absent).	High (if iodine not taken).
14. Iodine test.....	Ineffective.	Effective.
15. Goetsch test.....	Negative.	Positive.
16. Final test thyroidectomy...	Unsatisfactory.	Satisfactory.

and in patients whose ages varied from fourteen to fifty-seven years, showed that the basal metabolic rate ranged from 0 to 22 per cent with an average for the group of minus 13.7 per cent. Some patients have been seen suffering from both parkinsonism and hyperthyroidism. The importance of a proper diagnosis in such cases is evident, for if hyperthyroidism does not coexist, or if the metabolic rate is a false high reading, due to persistent tremor during the test, then thyroidectomy will further decrease the metabolism which in its basal state is already low. I have seen a few patients of this type who have been rendered myxedematous by such unwarranted operation on the thyroid gland. There is no easy way that one can arrive at a correct diagnosis in these borderline cases. It is important for the clinician to

plaints were extreme prostration, general body pains, vomiting and palpitation of the heart. The trouble had begun with an attack of influenza in February, 1932. She remained in bed for eight weeks suffering with generalized aching, especially in the back and legs, and a cough, nasal discharge and fever. In May, a month after she had recovered, she developed a "cold in the chest" which caused her to return to bed for a month. Two months later, in July, she began to complain of persistent palpitation of the heart and periods of mental confusion. Her exhaustion became more extreme and she had lost about 15 pounds despite a fair appetite. At this point, her physician had administered a course of iodides and digitalis, without any improvement in the pulse rate or nervousness. The mild mental aberrations and confusion were not aided by the use of the usual sedatives. About one week before her admission to the hospital, the patient had begun to vomit normal stomach contents after meals.

The patient had had two attacks of influenza during the postwar epidemics. Her general vigor and health had been very satisfactory until February, 1932. The family history was irrelevant.

When she was examined, the patient was lying quietly in bed but manifested considerable anxiety regarding her illness. In her attempts to talk she often seemed to be confused and would select the wrong words. The face showed a moderate masklike expression suggestive of early parkinsonism. The skin was definitely dehydrated. There was no flushing of the face and neck, no exophthalmos, lid lag or nystagmus. The pupils were equal, regular and slightly dilated but reacted normally to light and convergence. The tongue was coated and dry. The thyroid was slightly but definitely enlarged and was tender. It was very firm and of uniform consistency. No enlargement of the thyroid arteries could be demonstrated and no adenoma was felt. Tenderness in the bones was elicited, especially over the ribs.

The heart was normal save for the rapid rate, which varied from 100 to 160 beats per minute, but usually was approxi-

The significant neurological findings were as follows: (1) Inability to converge the eyeballs and a failure of pupillary contraction on near vision; (2) horizontal and rotatory nystagmus; (3) normal eyeground; (4) normal labyrinthine function; (5) parkinsonian mask (moderate grade); (6) slight exophthalmos; (7) coarse tremor of all extremities, increased by emotional excitement; and (8) normal gait without any disturbance in the concomitant movements in walking.

The laboratory findings were as follows: The basal metabolic rate was minus 27 and minus 10 per cent on two occasions. Slight tremor was noted during the tests. The Goetsch test was negative.

Examination of the spinal fluid revealed normal pressure, clear fluid, one cell per high-power field, and negative reactions to the Pandy test, the Wassermann test and the colloidal gold test.

Blood counts gave normal findings and concentration tests of renal function also yielded normal results.

This patient was referred to the clinic with a provisional diagnosis of hyperthyroidism. Apparently her physician had based his diagnosis on the presence of exophthalmos, goiter, tachycardia, loss of weight, tremor and a high basal metabolic rate. Following a complete study of her problem it became apparent that hyperthyroidism could be excluded. The history of an attack of influenza, the ocular signs (nystagmus and convergence defect), the type of tremor and the normal and even decreased metabolic rate were sufficient to establish the diagnosis of postencephalitic parkinsonism. The elevated basal metabolic rate, prior to admission, most certainly must have been produced by the tremor. It appears extremely unlikely that the low normal report at this clinic could have been the result of the iodine administration since the patient had not noted any subjective improvement. The physician was advised to continue medical management of the patient.

Case II. Thyroiditis with Acute Hyperthyroidism.—The patient, aged thirty-nine, was admitted by ambulance to the Clinic Hospital on September 11, 1952. Her main com-

results of urinalysis were normal, except for an occasional faint trace of albumin and an occasional leukocyte.

Blood counts were done repeatedly and always were normal. Blood chemistry studies showed the following: Fasting blood sugar, 116 mg. per hundred cubic centimeters; uric acid, 2.3 mg.; creatinin, 1.3 mg.; calcium, 12.74 mg.; and phosphorus, 4.6 mg. The Wassermann and Kahn serological tests were negative. The icterus index was 5. The blood agglutination tests for typhoid and undulant fever were negative. The total serum proteins were 6.57 mg., with albumin, 3.25 mg. and globulin, 3.32 mg.

This case presented a very difficult diagnostic problem. It was necessary to take into consideration the cause of the fever, abdominal pain and generalized hyperesthesia, the tachycardia and a goiter of an indurated and tender type, the high basal metabolic rate without definite signs of hyperthyroidism, and the features suggestive of a low-grade encephalitis. Early in the study pyelitis and acute abdominal inflammatory disease could be ruled out. In view of the normal blood findings various general infections could be eliminated from consideration. Therefore, it was possible to limit the study to the differential diagnosis between chronic encephalitis and thyroiditis with hyperthyroidism symptoms.

The main features favoring encephalitis were the history of an influenza-like infection, the mental aberrations, masklike facies and the diminished threshold for pain—possibly originating in the optic thalamus. On the other hand, the patient gave no history of excessive somnolence or diplopia; there were no residual ocular paralyses, nor was the tremor of the parkinsonian type. The muscular tone was normal and the reflexes were not diminished. The laboratory findings in the spinal fluid did not confirm such a diagnosis.

The case for thyroiditis and hyperthyroidism was much more plausible. The patient had tremor, persistent tachycardia and a high basal metabolic rate, with a firm, tender thyroid gland, which was slightly enlarged and gave the impression of tension of the capsule. There were, however, none of the car-

mately 130. Vagal pressure failed to produce any slowing of the cardiac rate. The electrocardiogram, on two occasions, showed a sinus tachycardia.

The abdominal examination showed very baffling physical signs. At different times tenderness and muscle spasm could be elicited, in any quadrant. Most commonly she had tenderness in the epigastrium or in the right lower quadrant. No tumor could be felt, nor was there any serious suspicion of an inflammatory lesion within the abdomen.

The pelvis showed marked tenderness of the uterus and both fornices, but no fixation or tumors. The rectum was normal. The extremities were generally tender to palpation. No edema, cyanosis or unusual flushing was observed. The biceps, triceps, patellar and Achilles reflexes were normal.

The neurological examination showed no abnormal reflexes. There was a fine wavering tremor of the extended hands, rather suggestive of weakness than of typical hyperthyroid tremor. The face lacked normal mimetic expression. The eyegrounds revealed slight haziness of the disks but this was well within normal limits.

The daily temperature record for the forty days of hospital observation showed a low-grade fever between 99 and 99.6 F. However, from the first to the sixth hospital day the fever rose steplike to 101.4 F. with a like decline in temperature to 99.5 F. Again between the twenty-first and thirtieth hospital days, the fever rose gradually to a fastigium of 102.2 F. and again declined to 99.5 F.

On three occasions, the basal metabolic rate was plus 24, plus 37, and plus 30 per cent, respectively. A spinal puncture showed that the initial pressure was 110 cm. of water, and after jugular compression was 200 cm. The arterial pulsations as well as the pressure rise and fall after jugular compression were normal. The fluid was clear, there were no cells, the Pandy and Wassermann tests were negative. Protein in the spinal fluid was 20 mg. and the colloidal gold test showed 1111100000. Two blood cultures were obtained and both were sterile. The

an influenzal infection six months before the onset of her present trouble. The family history was of no consequence.

The patient was emaciated and revealed a definite mask-like facies and a coarse tremor of the left hand and foot. The eyes showed moderate exophthalmos with a definite lid lag. The pupils reacted well to convergence as well as to light. There was no nystagmus or external ocular palsy. The eyegrounds were normal. The thyroid showed a moderate, diffuse enlargement (grade I) with moderate increase in firmness but no increase in vascularity.

The heart was moderately enlarged to the left with a pulse rate of 128 and a brachial blood pressure of 156 systolic and 70 diastolic. The cardiac rhythm was disturbed by frequent premature systoles but there was no fibrillation.

The positive neurological findings were parkinsonian mask-like facies; a partially open mouth, without drooling; bilateral exophthalmos; and a coarse tremor of the left arm and leg of wide excursion, increased by emotional excitement. There was no abnormality in the patient's reflexes or gait.

The first determination of the basal metabolic rate was plus 71 per cent, and the second, plus 111 per cent.

These readings were unsatisfactory inasmuch as the subject maintained a constant tremor during the tests. The urinalysis, blood chemistry determinations, blood counts and serological tests all gave normal findings.

This patient showed many of the features common to both postencephalitic parkinsonism and hyperthyroidism. Undoubtedly she had paralysis agitans. The metabolic rates had been persistently high, but obviously these could not be basal readings, in view of her tremor. Then, too, she had not improved following the use of iodine and roentgen radiation of the thyroid. After careful consideration, it was felt that a probable hypothyroidism following thyroidectomy would be detrimental rather than beneficial. She was advised to pursue medical treatment. This conclusion was based upon previous experience with such cases up to the year 1926. However, since that time we have seen many more patients who have presented these same

dinal signs of inflammation save swelling and tenderness. Thyroiditis, while rare, is known to result from acute infectious diseases, such as influenza. The argument against the thyrogenic source of the trouble was that the patient neither had the demeanor nor nervous manifestations of hyperthyroidism, nor did she show any appreciable response to three courses of iodine therapy.

Four weeks after leaving the hospital, the patient was seen at her home in a nearby village. At this time the physical signs were conclusive for hyperthyroidism; the notable changes were an increase in the fine tremor of the hands and the development of moderate exophthalmos. She was advised to take Lugol's solution again as a preoperative measure and then to submit to subtotal thyroidectomy. We have been informed that she made a satisfactory recovery following this operation.

Case III. Parkinson's Syndrome and Hyperthyroidism.—The patient, aged forty-one, came to the clinic for examination on July 6, 1926. Her principal complaints were nervousness, goiter, tremor, loss of weight and emotional upsets. The present illness began about sixteen years before with palpitation of the heart and nervous tremors. There was an indefinite history of influenza before the onset of her trouble, but there had been no symptoms of encephalitis. Likewise, there was no history of head injury or plumbism. She had received a course of "electrotherapy" for goiter, but the results had been disappointing.

About two years before admission, the nervous symptoms had increased. Her rest was disturbed by palpitation and dyspnea, and at times she was troubled with sweating and some diarrhea. She was given a course of iodine medication and later a series of roentgen irradiation of the thyroid without amelioration of her symptoms. The tremor became more pronounced and stiffness became noticeable in her legs and knees. Six months before coming to the clinic her basal metabolic readings had been plus 61 and plus 66 per cent.

The past history was negative for any chronic illness, toxemia or infection except the possibility that she may have had

an influenzal infection six months before the onset of her present trouble. The family history was of no consequence.

The patient was emaciated and revealed a definite mask-like facies and a coarse tremor of the left hand and foot. The eyes showed moderate exophthalmos with a definite lid lag. The pupils reacted well to convergence as well as to light. There was no nystagmus or external ocular palsy. The eyegrounds were normal. The thyroid showed a moderate, diffuse enlargement (grade I) with moderate increase in firmness but no increase in vascularity.

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problems and in none has the metabolic reading remained so persistently high, even in the presence of tremor. We also do not know how long the iodine had been administered before she was seen at the clinic. In hyperthyroidism, the most striking drop in metabolism usually takes place between the sixth and eighth day of iodine therapy.³ The radiation therapy, likewise, may have been insufficient to reduce the metabolic rate. I feel quite confident, therefore, that we should have advised thyroidectomy rather than general medical treatment. Unfortunately we have been unable to trace this patient or to learn of her subsequent course.

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poorly absorbed, if administered orally, it must be given in large doses if it is to be effective. Calcium lactate is a very useful form since it contains a great deal of calcium and is cheap. It can be given in doses of 1 drachm per day to 3 drachms every two or three hours. If one is to depend upon gastro-intestinal absorption, hypermotility must be prevented, so that no laxatives should be used. If calcium lactate causes diarrhea, as it does occasionally, calcium carbonate can be substituted and larger doses usually have to be used. Calcium gluconate, though it is more pleasant to take, contains less calcium and is more expensive. In an acute attack of tetany, nothing is more effective than the administration intravenously of 5 to 10 per cent solutions of calcium chloride in quantities of 10 to 20 cc. Great care should be exercised not to spill the calcium chloride into the tissues and for this reason a gravity method is useful, the calcium solution being preceded and followed by normal sodium chloride solution. Calcium gluconate, 10 cc. of a 10 per cent solution, is convenient for emergency use as there is less chance of causing a slough if some of it escapes the vein.

It is possible that the primary action of the parathyroids is to regulate the excretion of phosphates, since phosphate retention is one of the primary signs of parathyroid damage. When the phosphates are retained some of the previous availability of calcium is lost to the tissues. When parathyroid extract is administered, there is a sharp fall in phosphates in the serum, these are excreted in the urine, setting calcium free in the blood stream. The average diet contains more than sufficient phosphate and it is readily absorbed so that in the treatment of tetany, care should be exercised that the patient should not be given any medication containing phosphates. There are preparations on the market recommended by reputable drug houses for the treatment of tetany which contain large amounts of phosphates. In the treatment of tetany, factors which lower blood phosphates are useful and lactose may be used for this purpose.¹ This may be given in doses of 1 drachm per day to 2 drachms three times daily if it does not cause diarrhea.

In the average case of tetany, if sufficient calcium is given

REMARKS ON THE MANAGEMENT OF PARATHYROID TETANY

E. PERRY McCULLAGH

TETANY is not uncommon in medical practice. Pure parathyroid insufficiency, however, is rare except for those cases which appear postoperatively as a result of parathyroid damage during thyroidectomy.

Parathyroid tetany may be complicated by an element of idiopathic tetany which may obscure the diagnosis. Patients with idiopathic tetany ordinarily do not show any definite changes either in calcium or phosphorus metabolism or in any of the measurable substances in the blood, and they do not respond satisfactorily to the usual methods of treatment of parathyroid deficiency.

Parathyroid insufficiency may be simulated by hysteria, or attacks of carpopedal spasm may be precipitated by the alkalosis of vomiting or of hyperpnea, hysterical or otherwise. Sometimes epileptiform convulsions may be the first evidence of hypoparathyroidism and its presence may be overlooked, since this possibility as a cause of such convulsions may not be brought to mind. In some of the cases, the trophic changes dominate the clinical picture, and cataracts, nail changes or accumulation of fluid in the tissue spaces may not be ascribed to their true cause and hence the treatment may be improperly directed.

In acute postoperative tetany the diagnosis can be made before carpopedal or laryngeal spasms occur and frequently before the patient complains of any symptoms. At the first suggestion of parathyroid deficiency, the serum calcium and phosphorus in the blood are estimated and treatment is begun.

The symptoms of parathyroid tetany are caused by hyperirritability of the nerve cells due to loss of available calcium, the replacement of which is the key to treatment. Since calcium is

poorly absorbed, if administered orally, it must be given in large doses if it is to be effective. Calcium lactate is a very useful form since it contains a great deal of calcium and is cheap. It can be given in doses of 1 drachm per day to 3 drachms every two or three hours. If one is to depend upon gastro-intestinal absorption, hypermotility must be prevented, so that no laxatives should be used. If calcium lactate causes diarrhea, as it does occasionally, calcium carbonate can be substituted and larger doses usually have to be used. Calcium gluconate, though it is more pleasant to take, contains less calcium and is more expensive. In an acute attack of tetany, nothing is more effective than the administration intravenously of 5 to 10 per cent solutions of calcium chloride in quantities of 10 to 20 cc. Great care should be exercised not to spill the calcium chloride into the tissues and for this reason a gravity method is useful, the calcium solution being preceded and followed by normal sodium chloride solution. Calcium gluconate, 10 cc. of a 10 per cent solution, is convenient for emergency use as there is less chance of causing a slough if some of it escapes the vein.

It is possible that the primary action of the parathyroids is to regulate the excretion of phosphates, since phosphate retention is one of the primary signs of parathyroid damage. When the phosphates are retained some of the previous availability of calcium is lost to the tissues. When parathyroid extract is administered, there is a sharp fall in phosphates in the serum, these are excreted in the urine, setting calcium free in the blood stream. The average diet contains more than sufficient phosphate and it is readily absorbed so that in the treatment of tetany, care should be exercised that the patient should not be given any medication containing phosphates. There are preparations on the market recommended by reputable drug houses for the treatment of tetany which contain large amounts of phosphates. In the treatment of tetany, factors which lower blood phosphates are useful and lactose may be used for this purpose.¹ This may be given in doses of 1 drachm per day to 2 drachms three times daily if it does not cause diarrhea.

In the average case of tetany, if sufficient calcium is given

alone or with lactose, no additional treatment will be necessary. However, a few cases remain in which some parathyroid extract is required and if the calcium intake is high the amounts of parathyroid extract necessary will be small. Thus in a patient whose tetany became steadily worse while taking as much as 260 units per day of parathormone the symptoms are well controlled by 360 grains per day of a mixture half calcium lactate and half carbonate with 20 to 40 units of parathormone each week.

Parathyroid transplants in our hands have been of little or no value. The need for sedatives may arise occasionally and the value of substances which produce mild acidosis is very limited. In all cases, the treatment of tetany cannot be guided intelligently without the assistance of serum calcium and phosphorus estimations.

It should be remembered that vitamin D and parathyroid extract are alike in one respect, they raise the level of total serum calcium, but they are unlike in many respects. They are unlike in the matter of production of blood viscosity and in their effects on blood phosphates. Dogs die of hyperparathyroidism when the serum calcium is 15 to 16 mg. per hundred cubic centimeters, while vitamin D hypercalcemia with values around 20 mg. causes only slight illness in these animals.² Parathyroid extract and vitamin D should not be considered, therefore, as identical or even very similar substances in therapy. In practice, it has been our experience that patients receive more symptomatic benefit from ultraviolet light than they do from moderate doses of vitamin D orally.

Case I. Acute Postoperative Tetany.—A young woman, aged twenty-four, had a thyroidectomy for recurrent hyperthyroidism on August 29, 1933. The immediate postoperative reaction was slight. At nine o'clock on the morning of the first day afterward, the patient was found in a semireclining posture and seemed quite comfortable. It was noted, however, that the patient's arms were flexed at the elbows, her wrists flexed and her hands which were lying on her chest were held in a position highly suggestive of the typical carpal spasm of tetany.

There was no circumoral pallor, no suggestion of carp mouth, no twitching of the muscles was visible and there were no spasms of the toes nor paresthesias. On questioning it was found that she had had mild numbness in the feet during the preceding night. Chvostek's sign was mildly positive and Trousseau's sign was positive in two minutes with the sphygmomanometer cuff at 200 mm. of pressure. Blood was taken for serum calcium and phosphorus estimation. At one o'clock in the afternoon, distinct paresthesia was noted in the hands and mild though

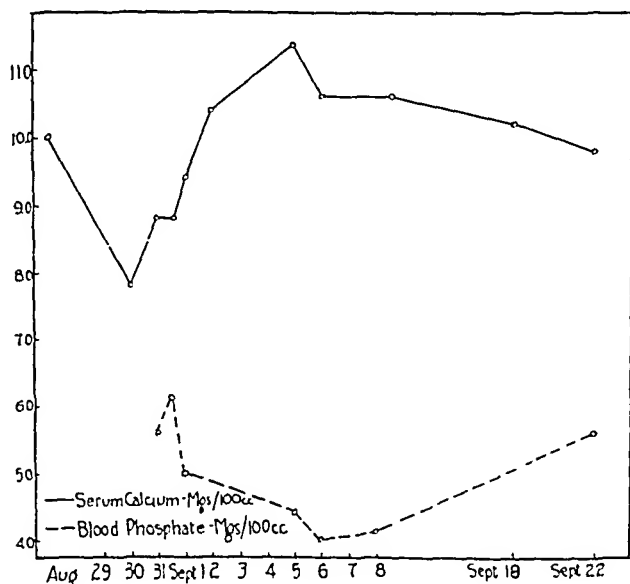


Fig. 169.—Chart showing serum calcium and phosphate in patient with tetany. (Case I.)

definite carpal spasm was present. Calcium therapy was begun by giving doses of 1 drachm of calcium lactate in water every four hours. The subsequent levels of serum calcium and phosphates in the blood may be followed on the accompanying chart (Fig. 169). The first line on the chart shows a fall in serum calcium from a presumed normal level of about 10 mg. per hundred cubic centimeters before operation to a level of 7.8 mg. on the first postoperative day. During the same period, the level of the blood phosphates was rising.

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Case I. Acute Postoperative Tetany.—A young woman, aged twenty-four, had a thyroidectomy for recurrent hyperthyroidism on August 29, 1933. The immediate postoperative reaction was slight. At nine o'clock on the morning of the first day afterward, the patient was found in a semireclining posture and seemed quite comfortable. It was noted, however, that the patient's arms were flexed at the elbows, her wrists flexed and her hands which were lying on her chest were held in a position highly suggestive of the typical carpal spasm of tetany.

acute tetany well controlled by treatment with calcium by mouth. It is typical also because the patient is a woman, for the disease is found at least twenty-five times as frequently in women as in men, whereas the proportion of males to females upon whom thyroid surgery is performed is about one to four. Tetany is more frequent after operation for recurrent hyperthyroidism, as in this case, and also is more severe in young than in old women, being especially aggravated at the time of the menses. Tetany may produce symptoms as in this instance when the total serum calcium is within normal range, if the phosphate level is high.

Case II. Chronic Postoperative Tetany with Generalized Convulsions and Trophic Disturbances.—A housewife, fifty-six years of age, entered the Cleveland Clinic in September, 1931. The unelicited history revealed only that she felt weak and tired and that for a year or more she had had some dyspnea on climbing stairs. Recently she had been unable to do her work and had been obliged to take almost complete rest. More complete history revealed that she had not felt completely well since a thyroidectomy in 1924. After that time she had experienced spells lasting about twenty minutes in which the hands were cramped and the feet at times felt drawn. Preceding each attack she recollected having numbness in the hands and blurring of the vision. During the preceding four years she had had three or four generalized convulsions; one or two of these were preceded by numbness in the hands and mild carpal spasm. Two of them, however, came on suddenly and she fell to the floor unconscious. According to her family, there was no clonic convulsion. Once she had involuntary micturition, but no involuntary defecation or biting of cheeks or tongue. Preceding such attacks her memory had been unusually poor and she was mentally dull. On two occasions, she was slightly disoriented, being unable to remember the day or hour, but was never completely disoriented as to place. The generalized convulsions were never remembered by the patient.

By 1925, the thumb nails and the nail on the left index finger had become grooved transversely, and very rough. The

On the morning of the second day there were no symptoms present but Chvostek's sign was mildly positive and Trousseau's sign was positive in thirty seconds at 200 mm. of pressure. The serum calcium on this day two hours after the administration of 1 drachm of calcium lactate was 8.8 mg. and the phosphates measured 5.4 mg. The dose of calcium lactate was then increased to a heaping teaspoonful every two hours and blood was again taken for calcium and phosphorus estimations two hours after three such doses. It showed the serum calcium to be 8.8 mg. and the phosphates, 6.1 mg. These large doses of calcium were continued from 8 A. M. to 8 P. M., six such doses having been given on the second day after operation and seven doses daily for the next six days, after which the number of doses was decreased to four per day and three days later to three each day, one dose before each meal. Each calcium and phosphorus level shown on the chart represents the value in blood taken two hours after the second or third dose of calcium for the day.

The patient was symptom-free from the second day after beginning calcium medication. On the third postoperative day, Chvostek's sign was still positive and Trousseau's sign appeared in three minutes on applying 200 mm. of pressure. Two days later, Chvostek's sign was absent and Trousseau's sign could not be elicited after 200 mm. of pressure for five minutes. Both signs were completely absent on the eighth and eleventh days after operation.

The patient remained symptom-free until the next menstrual period. The menstrual bleeding began three weeks after the operation. In the evening of the following day numbness and tingling and slight carpal spasm were noted and on the third day of the period she awakened with decided carpal spasm.

She took 4 drachms of calcium lactate at 8 A. M. and 4 drachms at 11.30 A. M. The symptoms were largely controlled but Chvostek's sign was positive and Trousseau's sign appeared in one-half minute at 200 mm. of pressure. Blood was taken at this time and showed a serum calcium of 9.8 and phosphates of 5.5 mg.

This is an example of a typical case of moderately severe

normal, fasting blood chemistry showed sugar 126 mg. per hundred cubic centimeters, urea 24 mg., creatinin 1.2, calcium 5.8 mg. per cent (total serum calcium done by Clarke's modification of the Kramer-Tisdall method). The total inorganic phosphates of the serum were 6.8 mg. per hundred cubic centimeters. The total serum proteins measured 5.25 per cent with the serum albumin 3.5 per cent and the serum globulin, 1.7 per cent. The basal metabolic rate was plus 1 per cent. The electrocardio-

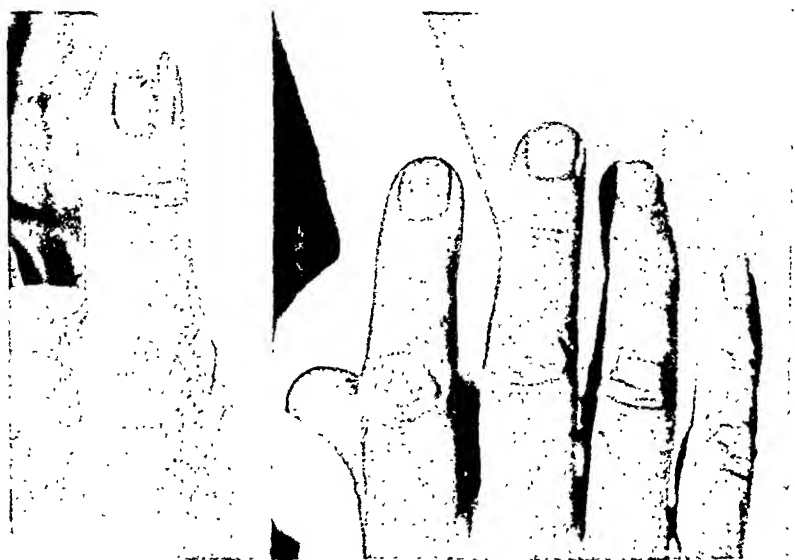


Fig. 170.—Trophic changes in finger nails of patient with parathyroid tetany. (Case II.)

gram showed inversion of T waves in lead I with flat T waves in leads II and III. The amplitude was low in all leads.

The phenolsulphonphthalein test for kidney function showed 50 per cent excretion of the dye in two hours. An average of two urea clearance tests was 72.5 per cent clearance hourly. Fractional gastric analysis revealed no free hydrochloric acid.

The roentgenographic examination showed evidence of decalcification of the bones, which was more marked in the right hand, wrist and forearm than in the legs or feet. The bones were less dense than those of a woman of her own age taken on

surrounding tissue appeared normal. The scales treated with potassium hydroxide showed no fungi but the diagnosis of fungous infection of the nails had been made by a competent dermatologist who did not suspect tetany. Postoperative tetany had been diagnosed in 1925 by one physician but intermittent treatment consisting of 15 grains of calcium lactate three times per day had been the only measure employed.

Her sight gradually became worse and in December, 1926, a cataract was removed from the right eye, and another from the left in October, 1927. On both occasions the diagnosis was senile cataract, and tetany had not been suspected.

Examination in September, 1931, revealed a pasty, pale woman who looked older than her age, which was fifty-six years. The eyes showed evidence of bilateral iridectomy. She was dull mentally. The lower teeth were present and were not loose. The pulse rate was 120 and regular. The blood pressure was 140 systolic, 84 diastolic. The heart was enlarged to the left and there was a relative cardiac dullness extending 3.5 cm. to the right and 11.5 cm. to the left of the midline. The sounds were of good quality. She was dyspneic. Percussion of the chest revealed diminished resonance in the lower half on both sides and the breath sound were distant there. There were moist râles throughout both sides. The liver was not enlarged. There was pitting edema as high as the waist and slight edema was visible about the chest after using the stethoscope. The nails of the thumbs, index and middle fingers and great toes were thickened, very rough, pitted and had rather deep transverse grooves. The condition appeared to start at the base and the nails were not as friable as is usual with fungous infections (Fig. 170). Chvostek's and Trousseau's signs were strongly positive.

The cardiac changes did not appear sufficient to explain the edema and since the diet had included meat only once in two weeks and an egg every third day and a glass of milk daily, a nutritional origin for the edema was considered.

Laboratory Tests.—The urine varied in specific gravity from 1.008 to 1.033. It contained from 2 plus to 4 plus albumin, many hyaline and a few granular casts. The blood counts were

doses of calcium, improvement was obvious. The calcium, however, failed to rise higher than 7.7 mg. per hundred cubic centimeters and the phosphate level tended to climb again, presumably as the effects of the parathormone were completely lost.

After the introduction of parathormone again in doses varying from 10 units per day at first to 20 units each week the serum

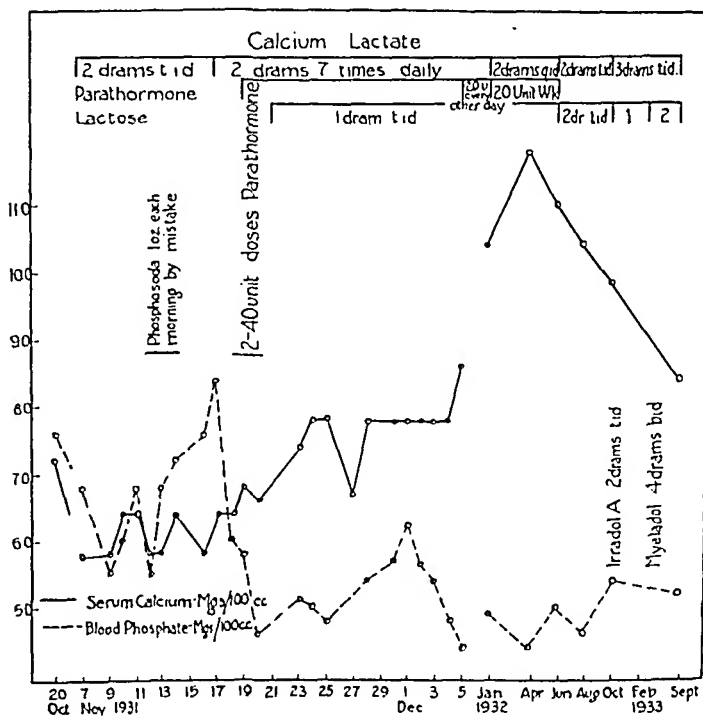


Fig. 171.—Chart showing medication and levels of calcium and phosphate in the blood of patient with tetany. (Case II.)

(Parathormone is the trade name for Collip's parathyroid extract prepared by Eli Lilly Co.)

calcium later rose as high as 10.9 mg. per hundred cubic centimeters. This level was considered unnecessarily high, so parathyroid extract was discontinued on June 19, 1932. The serum calcium remained normal without parathormone until after October 19, 1932. In May, 1933, the serum calcium level was somewhat lower than normal although the patient was still

the same plate, but were not thought to show more decalcification than might have been caused by disuse.

A roentgenogram of the chest revealed signs of considerable fibrous and some exudative infiltration bilaterally and was interpreted as showing thickening of the pleura at the left base with probable effusion.

The patient entered the hospital on November 7, 1931, and was there until December 5, 1931. In order to determine the relative importance of the hypoproteinemia and of the hypocalcemia in the production of symptoms and signs it was decided to treat only the calcium disorder at first. Therefore the patient continued to take a low-protein diet similar to the one she had had before hospitalization. She was allowed no meat, fish, eggs, cheese or gelatin but was given two glasses of milk per day.

Calcium was administered by mouth in the form of calcium lactate. At first, 2 drachms three times a day was given, but the amount was later increased by giving the same dose every two hours for twelve hours during the day. Later, parathormone, 40 units daily, was added. About a week after treatment had begun, phosphate of soda was inadvertently administered through the mistake of an intern. This was given for three days, November 12 to November 14, 1931, with a demonstrable effect on the serum phosphate curve.

The amounts of calcium and parathyroid extract were gradually decreased during the patient's stay in the hospital. After the patient had been on this regimen for two months, the protein intake was no longer restricted.

The calcium and phosphate levels as well as the amounts of calcium administered are shown in the accompanying chart (Fig. 171). At first, between November 7, and November 12, 1931, when the patient was acutely ill, calcium lactate, 2 drachms three times a day, was insufficient in itself to change the levels of the serum calcium and phosphorus materially. When the phosphates were given in error a marked rise in phosphates was very apparent, demonstrating the ease with which these substances are absorbed as compared to calcium. After two relatively large doses of parathormone and with larger

Since November 20, 1931, a positive Chvostek's sign has not been seen and on every observation since January, 1932, Trousseau's sign has been absent even after 200 mm. of pressure for five minutes. She has gradually gained weight, and weighed 120 pounds on May 18, 1933.

This case serves to show an extreme example of chronic tetany. It demonstrates that chronic tetany may be mistaken for other conditions because of trophic changes produced in the nails and the lenses. The peculiar mental changes and disorientation are uncommon features but are seen occasionally. Such generalized convulsions as these may be mistaken for idiopathic epilepsy.

The clinical evidence in this case points strongly to the possibility that edema in chronic tetany can be due to degenerative changes in the renal tubules since the evidence of kidney damage here was chiefly that of massive loss of protein from the renal system. The fact that such loss of protein stopped almost completely after correction of the calcium metabolism, while the patient was still on a low-protein intake, tends to strengthen the view that such changes may be caused by the calcium deficiency. In this case there is also undoubtedly myocardial weakness but the albuminuria, pleural effusion and edema have not tended to reappear on moderate exercise, much more than she was taking previously, so long as the calcium metabolism remains near normal.

The justification for persisting so long with treatment consisting of calcium by mouth alone or with lactose is that most cases can be controlled well by one or both of these measures without parathyroid extract. When this is true, rapid changes produced by intravenous administration of calcium or parathyroid extract early during the course of observation serve only to prolong the time in which the simplest, cheapest yet most effective form of treatment can be estimated.

Both ultraviolet light and vitamin D were employed in the treatment and the effects of both are considered useful, though indirect and relatively unimportant.

symptom-free. It appears that this patient will require small amounts of parathormone from time to time.

Additional treatment consisted of thoracentesis which was done seven times while the patient was in the hospital, and on each occasion except the last, from 500 to 1300 cc. of fluid was withdrawn from the chest. The specimens of fluid varied from 1.012 to 1.014 in specific gravity, red cell count varied from 550 to 840 and leukocyte count, which was 90 per cent lymphocytes, from 340 to 1060. The protein content varied from 2.4 to 4 Gm. per 100 cc. No organisms were found and cultures were sterile.

The urine was free from casts after November 16, 1931, and was free from albumin on December 3, 1931. A faint trace of albumin has been found from time to time since.

The total serum protein on November 11, 1931, was 5.25 with 3.53 per cent albumin and 1.72 per cent globulin. On November 19th, the total percentage of protein was 6.12 with 2.17 per cent albumin and 3.95 per cent globulin. Two months later the albumin was 4.03 per cent, globulin, 4.12 per cent and the total protein 8.15 per cent. Basal metabolism on January 20, 1932, was plus 6 and plus 8 per cent.

The electrocardiogram on January 20, 1932, showed a poor offset of T waves in all leads. T waves were flat in leads I and of low amplitude in lead II. There was slight notching of Q.R.S. complexes without prolongation of conduction time.

The patient was symptom-free from November 20, 1931 on, having had mild paresthesiae and carpal spasms when the serum phosphates rose higher than 7 mg. per hundred cubic centimeters. As the edema disappeared, she lost weight, from 133 pounds on November 7th to 91 pounds on January 20th. By the latter date there had been no clinical evidence of pleural effusion for six weeks and the edema had disappeared completely. At that time, the appearance of the nails was almost entirely normal. The cardiac enlargement has persisted but in September, 1933, no edema had been seen for eight months. She has been able to do her housework regularly. The blood pressure has varied between 170 systolic and 100 diastolic on June 9, 1932, to 125 systolic, 70 diastolic on February 28, 1933.

her husband, who was a physician, considerable alarm. It was also disclosed that she had frequent slight paresthesias of the hands, a tendency to be cold and to have a dry skin and somewhat brittle nails. She lacked energy and endurance and was less alert mentally than normally.

Examination on December 4, 1931, showed a well-nourished woman, aged thirty-six years. The pulse rate was 60. There were no lens opacities. The tonsils had been removed. There were several dental fillings. The laryngeal examination showed no abnormality. There was no Chvostek's sign but Trousseau's sign was positive in one and one-half minutes with the sphygmomanometer cuff in place at 200 mm. of pressure. The thyroidectomy scar was healthy and no excess thyroid tissue palpable. There was a healthy abdominal scar which marked the site of unilateral oophorectomy in 1918. The remainder of the physical examination showed no abnormalities. The basal metabolic rate was minus 28 per cent, the serum calcium, 10.6 mg., and the blood phosphates, 2.6 mg. per cent.

A diagnosis of hyperthyroidism and hypoparathyroidism was made, and the fact that the patient's serum calcium and phosphate levels were normal was remarked upon as being most unusual. It was suggested that she take 3 grains (Parke, Davis and Co.) per day of desiccated thyroid, a dose about five times as great as she had been taking, and 60 grains of calcium lactate powder twice a day.

The patient returned for observation on December 26, 1931. The desiccated thyroid had been increased to 4 grains each day. She felt more energetic, more alert mentally and was not drowsy. She still felt cold, however, and the skin, though improved, was still abnormally dry and the nails were brittle. There were paresthesiae in the hands on walking and she had had three severe attacks of laryngeal spasm, in spite of continuation of 120 grains daily of calcium lactate. On this date the basal metabolic rate was minus 16 per cent. The Chvostek's sign was negative but Trousseau's sign was present. It was suggested that the dose of calcium be increased to 240 grains

There is a small group of patients with postoperative parathyroid tetany in which tetanic spasms occur when the total serum calcium is normal. It is usually in the lower limits of normal, however, and the blood phosphates are high. In such cases complete relief from both chronic and recurrent acute attacks is afforded by the proper application of calcium therapy alone or in conjunction with lactose or parathyroid extract, ultraviolet radiation of vitamin D by mouth.

In pure idiopathic tetany in adults the calcium and phosphorus levels in the blood are normal during an attack and no relief may be obtained either by administration of large doses of calcium orally or intravenously or by parathyroid extracts.

The type of case I shall describe here differs from both of the above groups for it represents a type in which the calcium and phosphorus levels are always well within normal range. Severe attacks of tetany recur in spite of this and yet each attack can be controlled by intravenous calcium. Oral calcium and lactose therapy, parathyroid extracts and ultraviolet light are of decided benefit but they do not give complete relief. The presence of an hysterical element in such cases is difficult to rule out.

Case III. Mixed Type of Tetany.—The patient, a woman, when thirty years of age had had a thyroidectomy performed in two stages for severe hyperthyroidism in November, 1925. The basal metabolism had been plus 57 per cent before operation and the pulse rate 140. The pulse rate had fallen to 90 by the eighth day after operation and later she had gained 20 pounds. By January, 1927, her weight had increased a total of 29 pounds in spite of dietary restrictions and she complained of dryness of the skin and a constant sense of coldness. She continued taking small amounts of thyroid from that time until she was seen in the Cleveland Clinic in December, 1931, when she was taking daily 3 grains of thyroid (Burroughs and Wellcome).

At that time it developed that she had had mild carpal spasm at times for three years and in the few months preceding December, 1931, she had had repeated attacks of severe laryngeal spasm which at times were severe enough to cause

cent, the serum calcium, 10.2 mg. and the phosphates 2.9 mg. There were two devitalized teeth which showed periapical absorption. She was advised to have them removed. This was done immediately after she had had 10 cc. of a 10 per cent solution of calcium gluconate administered intravenously. She was instructed to change the calcium medication to calcium lactate, 360 grains per day, and to keep an accurate temperature record.

On July 3, 1933, the patient had had a daily rise in temperature of 99 to 100 F. for several weeks. In spite of the very large doses of calcium she had had four severe attacks of tetany. Rechecking the former examination failed to reveal any certain cause for the mild fever. Chvostek's and Trousseau's signs were positive and the serum calcium had risen to 11.7 mg. and the phosphates had fallen to 2.7 mg. Parathormone, $\frac{1}{2}$ cc. every second day, was added to the treatment and on July 28th she had had no more seizures.

The rather detailed recital of progress in this case serves perhaps to illustrate a very apparent relationship between calcium therapy and the relief from tetanic seizures of which the patient complained. This together with the fact that the tetany occurred after thyroidectomy is highly suggestive of an element of parathyroid insufficiency. There are many features which point toward the nonparathyroid origin of tetany such as this: First, the fact that the symptoms were not present immediately after operation; second, the fact that they are associated with calcium and phosphorus levels constantly within the normal range. These facts in addition to the incomplete control of symptoms makes it almost certain that in this case the tetany is not purely of parathyroid origin. I have seen a small group of thyroidectomized patients who have tetany associated with normal calcium and phosphorus levels and yet at the same time have obtained definite relief from calcium therapy. Other patients with idiopathic tetany show no improvement on calcium therapy. It would seem that such cases are examples of a mixed type of tetany partly originating from parathyroid deficiency, and partly of idiopathic origin.

per day and that generalized irradiation with ultraviolet rays be used daily.

On February 25, 1932, the patient reported that she had been completely symptom-free. Numbness of the hands had returned for one week when she had discontinued the use of the calcium. There were no signs of hypothyroidism. The Chvostek's sign was negative, and Trousseau's sign was negative in five minutes at 200 mm. of pressure. The basal metabolic rate was plus 4 per cent. The serum calcium was 10.9 and the phosphates 3. She was advised to continue the daily use of ultraviolet light and to use 4 grains of desiccated thyroid and 180 grains of calcium lactate daily.

On August 20, 1932, the same measures having been continued, the patient was symptom-free except for slight drowsiness and slight edema of the lids. Trousseau's sign was positive. The pulse was 56, the basal metabolic rate minus 15 per cent. The serum calcium was 10.7 and the phosphates 4.2. No change in treatment was suggested.

On February 23, 1933, she was symptom-free and still taking 4 grains of desiccated thyroid per day. For several months she had been taking 120 grains of calcium lactate and 180 Gm. of lactose daily, and had continued the use of ultraviolet light. Trousseau's sign was positive in two minutes at 200 mm. of pressure. Chvostek's sign was negative. The basal metabolic rate was minus 9 per cent and the serum calcium 10.6 and the phosphates 2.9 mg. per cent.

On May 25, 1933, this regimen had been continued, but the patient had had three severe attacks of tetany with laryngeal spasm. Each of these was relieved promptly by the intravenous injection of 10 cc. of a 10 per cent solution of calcium gluconate.

Physical examination was entirely negative except for slight hyperemia of the optic disks, filled teeth, and a positive Chvostek's and Trousseau's sign. Special nose and throat examination, blood counts, urinalysis, culture of the urine for tuberculosis, undulant fever and agglutination tests showed no abnormal findings. The basal metabolic rate was minus 16 per

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appear or are late and may appear only partially, axillary and pubic hair may be scanty, anal hair is scant or absent, the beard may be scant or absent and general body hair may be present in very small amounts. Growth is decidedly altered in pronounced cases, the larynx fails to attain adult proportions and the voice is high. The epiphyses do not close at the normal age and the arms and legs become unusually long. The span may exceed the height and the leg length exceed sitting height, producing the typical eunuchoid proportions. In such cases, libido and potency may be normal. Orgasm and a small ejaculation may occur even in advanced cases but there is aspermia. The mentality is often excellent, though the general appearance remains youthful.

In cases of castration or functional hypogonadism in the adult, the prostate atrophies markedly in advanced cases, although such atrophy may not be pronounced for months after castration. The penis shows some atrophy but to a lesser degree. The growth of hair may not be greatly altered, even in castrates, although some change in body hair is the rule. Hair may be lost entirely from the chest and become scant on the arms and legs. Axillary, anal and pubic hair may be very sparse, the latter of female distribution. There is a tendency to increased body weight, the fat being distributed chiefly about the abdomen and the breasts. The skin often is sallow and has an atrophic appearance. Complete or partial impotence is the rule or in the presence of potency, partial or complete aspermia is likely to occur. Sexual libido tends to be diminished. Some patients complain of nervousness and loss of energy although these may not be noted, even in castrates. Vasomotor disorders occur in some cases and sudden hot flashes similar to those seen in the female at the menopause may occur. A tendency of spells of dizziness and mental depression have been noted in some cases.

Laboratory tests show a common tendency to hypometabolism. The glucose tolerance apparently is not consistently altered. Total serum calcium and total blood phosphate estimations have been found normal in castrates but the blood

HYPOGONADISM IN THE ADULT MALE FOLLOWING BILATERAL HERNIORRHAPHY

E. PERRY McCULLAGH

HYPOGONADISM in men is a relatively common condition and even excluding the hypogonadism which is so frequently the result of pituitary disease, the condition is still not rare. It is seen in those patients who have had bilateral orchidectomy performed, it may be seen following local injury, or may be caused by interference with the blood supply such as that following bilateral herniorrhaphy, as in the cases reported here. In addition to these, there is another group in which pituitary sex hormones appear to be present in adequate amount, there is nothing in the history to suggest a cause for testicular damage, and yet there are distinct evidences of hypogonadism and repeated assays for the internal secretion of the testes show a marked diminution or absence of this substance. In any of these groups except the castrates it may be difficult, if not impossible, to reach a diagnosis with a reasonable degree of accuracy without the assistance of bio-assays.

Hypogonadism in the adult offers a somewhat more difficult problem in diagnosis than is presented in the cases in which it antedates puberty. This is chiefly because when the genitalia and secondary sex characteristics and growth have attained their normal adult state there are fewer visible changes to be observed. The symptoms themselves, though relatively constant, are at the same time notoriously misleading in some cases. Sexual impotence, for instance, though a common symptom in hypogonadism, also occurs in many cases in which no testicular deficiency is present. On the other hand, severe testicular deficiency may be present without accompanying impotence.

When hypogonadism appears before puberty, the genitalia do not grow to their normal size. Both penis and prostate may be obviously small, secondary sexual characteristics do not

appear or are late and may appear only partially, axillary and pubic hair may be scanty, anal hair is scant or absent, the beard may be scant or absent and general body hair may be present in very small amounts. Growth is decidedly altered in pronounced cases, the larynx fails to attain adult proportions and the voice is high. The epiphyses do not close at the normal age and the arms and legs become unusually long. The span may exceed the height and the leg length exceed sitting height, producing the typical eunuchoid proportions. In such cases, libido and potency may be normal. Orgasm and a small ejaculation may occur even in advanced cases but there is aspermia. The mentality is often excellent, though the general appearance remains youthful.

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Laboratory tests show a common tendency to hypometabolism. The glucose tolerance apparently is not consistently altered. Total serum calcium and total blood phosphate estimations have been found normal in castrates but the blood

cholesterol was found to be high in three of eight castrated men, and this may be found in cases of hypogonadism from other causes. There also is a tendency to an increase over normal amounts of pituitary sex hormone. The final evidence of hypogonadism lies in the repeated demonstration of less than normal quantities of testicular hormone in the blood or urine or both.

In the treatment of such cases, encouraging results have been obtained by the administration of a preparation of "comb-growth-promoting substance" from male urine which has been prepared in our laboratories by D. R. McCullagh and which has been called "androtin." This is believed to be a testicular hormone, although unequivocal proof is not yet at hand. This substance is capable of preventing the changes produced by castration in animals excepting perhaps the hypertrophy of the pituitary gland which is an accompaniment of castration. Injection of purified bull testis extracts, according to Moore,² is incapable of preventing the appearance of castration cells in the pituitary glands of castrated male rats. This hypertrophy, however, can be prevented by the injection of testicular pulp in the animals according to the work of Martins and Rocha.³ Such injections were made into the castrated male of a pair of parabiologic twins and by such injections, precocious puberty was prevented in the normal female partner. This difference between testicular pulp and purified testicular or urinary extracts has been interpreted by postulating the possible presence of a second testicular hormone.⁴ Other experiments, chiefly those of Martins and Rocha, point toward such a possibility. It should not be forgotten that the same or a comb-growth-promoting substance is found in the urine of women.

The method of assay of body fluids for testicular hormone in use in our laboratories has been described in detail previously.¹ It consists of boiling a forty-eight-hour acidified specimen of urine for eight hours with chloroform, after which the chloroform extract is separated from the urine and taken up in oil. This extract is divided into four equal parts, one part

being injected into each of two caponized roosters on each of two consecutive days. The resultant total comb growth (length plus height) serves as an index of testicular hormonal activity. Extraction by this method is incomplete but so standardized that the results are constant and comparable. The capon's combs must have regressed fully and be stationary and the growth after injection of the hormone must be followed by regression of the comb. Certain other precautions must be observed in the care of the test birds. The average comb growth produced by the extract from the urine of normal men under sixty years of age is 5.5 mm. In practice, if one assay using two birds shows a high normal value in each, it is usually considered that further assays are unnecessary. If, however, one assay shows levels below normal or if no hormone at all can be detected, it becomes necessary to repeat the test until a total of four to eight birds have been used. This method of assay is very similar to that of Funk, Harrow and Lejwa.⁵

In the preparation of hormone for clinical use, large quantities of urine must be processed and a much more refined product is prepared than that which is used for assay alone. The preparations used are in oil and are standardized to contain from 6 to 40 bird units per cubic centimeter. One bird unit is considered to be that amount of hormone which when injected into a capon on each of two consecutive days produces from 2 to 4 mm. of comb growth. Eight or ten birds are used for assay of a product to be used for therapy.

The following cases are typical examples of hypogonadism in adult noncastrated males and demonstrate the appearance of this state following bilateral herniorrhaphy.

Case I.—The patient, a married man, aged fifty-one, was seen in August, 1932. Bilateral inguinal herniorrhaphy had been done in July, 1928. Before that date he had had partial impotence but since then it had become almost complete, though sexual libido persisted. He still had an occasional nocturnal emission. His energy was definitely diminished and he could no longer carry on his occupation as chauffeur without

cholesterol was found to be high in three of eight castrated men, and this may be found in cases of hypogonadism from other causes. There also is a tendency to an increase over normal amounts of pituitary sex hormone. The final evidence of hypogonadism lies in the repeated demonstration of less than normal quantities of testicular hormone in the blood or urine or both.

In the treatment of such cases, encouraging results have been obtained by the administration of a preparation of "comb-growth-promoting substance" from male urine which has been prepared in our laboratories by D. R. McCullagh and which has been called "androtin." This is believed to be a testicular hormone, although unequivocal proof is not yet at hand. This substance is capable of preventing the changes produced by castration in animals excepting perhaps the hypertrophy of the pituitary gland which is an accompaniment of castration. Injection of purified bull testis extracts, according to Moore,² is incapable of preventing the appearance of castration cells in the pituitary glands of castrated male rats. This hypertrophy, however, can be prevented by the injection of testicular pulp in the animals according to the work of Martins and Rocha.³ Such injections were made into the castrated male of a pair of parabiotic twins and by such injections, precocious puberty was prevented in the normal female partner. This difference between testicular pulp and purified testicular or urinary extracts has been interpreted by postulating the possible presence of a second testicular hormone.⁴ Other experiments, chiefly those of Martins and Rocha, point toward such a possibility. It should not be forgotten that the same or a comb-growth-promoting substance is found in the urine of women.

The method of assay of body fluids for testicular hormone in use in our laboratories has been described in detail previously.¹ It consists of boiling a forty-eight-hour acidified specimen of urine for eight hours with chloroform, after which the chloroform extract is separated from the urine and taken up in oil. This extract is divided into four equal parts, one part

On the basis of these assays, the diagnosis of hypogonadism seemed justified. The only treatment prescribed was 1 cc. of androtin (15 bird units per cubic centimeter) every second day, which was given regularly from September 9th to November 8th. Symptomatic improvement began after the fourth dose. The patient was seen December 3rd and reported that he had more energy, the nervousness had diminished definitely and he slept more normally. Erections occurred normally for the most part, although occasionally these were incomplete. Normal sexual intercourse had been possible repeatedly. The pulse was 82, the blood pressure 115 systolic, 80 diastolic and the temperature 98 F.

He was advised to continue with this therapy and took 1 cc. of androtin daily for four days, and then 1 cc. every second day for sixteen doses. Unfortunately no further assays or basal metabolism estimations could be arranged, but he was symptom-free when last seen in March, 1933.

Case II.—A man, aged thirty-seven, presented himself for examination on April 6, 1933, because of sexual impotence. He had had a left inguinal herniorrhaphy in 1913, a right inguinal herniorrhaphy in 1919. Right herniorrhaphy was performed again in 1929 and in July, 1932, bilateral herniorrhaphy was performed using strips of fascia as sutures. Following the last operation, bilateral testicular swelling had occurred and lasted for about a week, following which the testes atrophied markedly.

He had known himself to be both potent and fertile previously and in August, 1932, was married. Erection had occurred on only two occasions following marriage and was followed only once by ejaculation. Once a nocturnal emission had occurred. Apart from this only a few partial erections had occurred. He had gained 20 pounds, and the excess fat accumulated chiefly about the abdomen. He complained of repeated spells of dizziness and said that his energy had been noticeably diminished. He had noticed no nervousness, no flashes of heat and no change in the rate of growth of the beard. The amount of hair on the chest had diminished definitely according to the

considerable fatigue. He complained of being too nervous and had worried somewhat about his impotence. There had been no gain in weight, no change in the beard or body hair had been noted, and he had had no flashes of heat. There was no tendency to paresthesia, dryness of skin, hair, nails, edema, drowsiness or other symptoms or signs suggestive of hypothyroidism.

The physical examination revealed the following: The patient's height was $69\frac{3}{4}$ inches; his weight, 146 pounds; the temperature, 98 F.; the pulse rate 64; and blood pressure, 115 systolic, 75 diastolic. A mild prostatitis had been diagnosed in 1930 and had been treated by massage at intervals since then, but never more than 15 white blood cells per high-power field had been demonstrated. The prostate itself was not demonstrably atrophied by rectal palpation and was symmetrical and soft. The penis was normal. The testes were smaller than average and there was a slight bilateral varicocele. Verumontanitis as a possible cause of impotence had been ruled out by cystoscopy. Distribution of hair was normal. The skin looked pale and slightly atrophic.

The basal metabolic rate on two occasions was minus 23 and minus 28 per cent. The urinalysis, blood counts, blood sugar, urea, uric acid, creatinine and nonprotein nitrogen were normal. The serum calcium was 10.7 mg. per cent and the blood phosphates 3.1 mg. The blood cholesterol was 214 mg. The serum proteins totaled 6.7 per cent with the albumin 4.4 and the globulin 2.3. The blood Wassermann and Kahn tests were negative.

The assay for testicular hormone was made with 50 cc. of blood. The first test bird showed a comb growth of 2 mm. in one day after injection of the extract and 2 mm. in four days in a second capon. This result was regarded as a low normal. A forty-eight-hour specimen of urine was assayed giving 2 mm. of comb growth in four days in one bird and 2 mm. in two days in a second. A second assay with forty-eight-hour urine was made and all the extract was injected into one bird which was known to be dependable with a resultant comb growth of only 1 mm.

was soft. The left testis was smaller and very soft with indefinable borders. The prostate was distinctly smaller than average and quite solid. A small amount of watery secretion was obtained for examination. It showed no sperms, many lecithin bodies, and an occasional prostatic cell and leukocyte. Because of the impotence no specimen of semen could be obtained artificially or by coitus.

Bio-assay for anterior pituitary sex hormone by Friedman's modification of the Aschheim-Zondek test showed mature follicles 2 plus and congestion of the uterus 2 plus. This result is considered as indicating a measurable, though not definitely increased, amount of this substance. No quantitative assays for this hormone were made. Assay for testicular hormone by the method already described showed 2 mm. comb growth in two days in the first bird and the same in a second. A repetition of this assay gave 1 mm. growth in one capon and none in a second. This test showed that the patient had distinctly less than normal amounts of testicular hormone.

The basal metabolic rate on two occasions was minus 13 and minus 22 per cent respectively. A roentgenogram of the sella turcica was normal. Urinalysis, blood counts, blood Wassermann and Kahn tests were normal. The blood sugar was 81 mg. per hundred cubic centimeters five hours after eating. The blood urea was 39 mg.; calcium 11.1 mg.; phosphates 3.4 mg.; and cholesterol, 222 mg.

Treatment was begun on April 22, 1933. The patient was supplied with a preparation of androtin containing 15 units per cubic centimeter. He received $\frac{1}{2}$ cc. intramuscularly in the gluteal region every second day until May 12th with no distinct improvement. He then took 1 cc. every second day of a preparation containing 6 units per cubic centimeter for six doses, then 2 cc. (12 units) every second day for three additional doses, still without any remarkable symptomatic relief. A special preparation was then made which contained 40 units per cubic centimeter. Of this he received $\frac{1}{2}$ cc. every second day with some irregularity, but 800 units were given in this way between May 18th and August 16th.

patient. The amount and distribution of body hair was not noticeably altered otherwise.

He was a healthy-looking, obese man, whose height was 66 inches and weight 187 pounds (Fig. 172). The pulse rate was 74, the temperature 97.8 F. and blood pressure, 132 systolic and

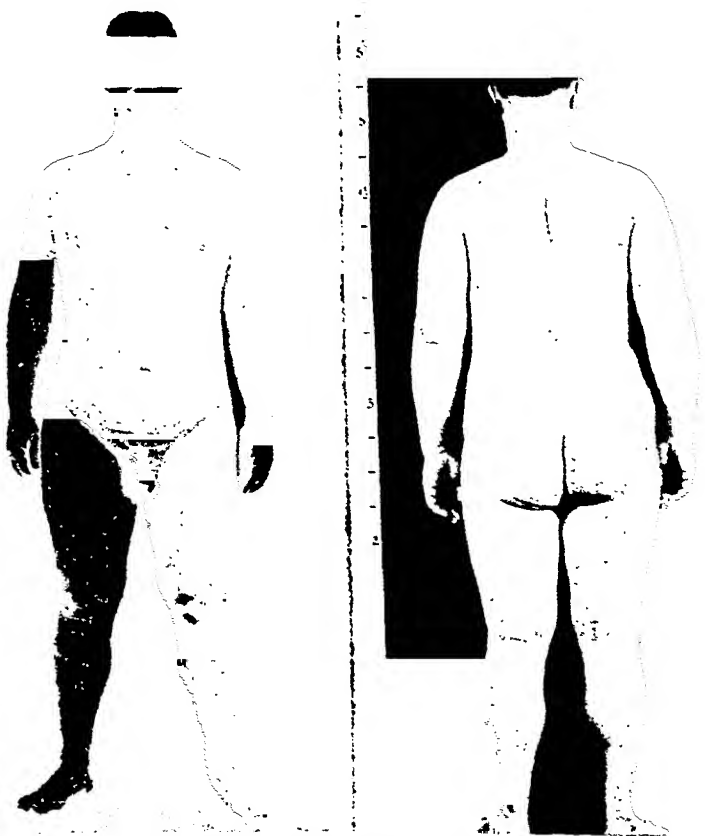


Fig. 172.—Photograph of patient with hypogonadism. (Case II.)

84 diastolic. The body weight was distributed in a way which gave him an appearance suggesting a pituitary type of obesity. The skin was fine in texture and appeared to be normal. The hair on the body and head seemed normal. The penis was normal, but both testes were obviously atrophic. The right one was about 2 cm. in length and 1 cm. in width and its consistence

Until the latter half of this period of treatment, no distinct subjective improvement was noted. After that, there was a gradual reappearance of erections, energy was increased and normal intercourse was accomplished on several occasions, though this had been impossible previously for more than a year. Withdrawal of treatment was followed by recurrence of the symptoms, although this was done without the patient's knowledge, injections of sterile oil having been used.

DISCUSSION

The psychic factor in such cases is impossible to rule out completely. It has been our experience, however, that patients who apparently have a less complete hypogonadism tend to get beneficial results with smaller doses of the extract, whereas those with a severe grade of the condition are improved only slightly, not at all, or only after the use of very large doses. This observation is quite consistent with the common experience with replacement therapy in other endocrine deficiencies.

In the second case reported here the fact that there was no improvement on moderate doses of the extract, whereas improvement appeared after the use of a more potent extract suggests a nonpsychic factor. This is also supported to some extent by the fact that the symptoms recurred on withdrawal of the treatment.

It is obvious that if hypogonadism in men is to be treated satisfactorily, the extent of the hormonal deficiency must be known, and hence methods of bio-assay become increasingly important as aids in diagnosis.

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appeared fairly frequently who had marked hypoglycemia and yet felt perfectly well, and had no sign of a reaction. Or to complicate the picture still further, the same patient might develop the symptoms when his blood sugar was 70 mg. per cent and at another time, when he felt well and had no symptoms, the blood sugar might be as low as 38 mg. per cent. Why should one patient have so many symptoms with hypoglycemia and another none? Is it really hypoglycemia *per se* which causes the symptoms? These are paradoxical findings for which no one has yet given any satisfactory explanation.

Hyperinsulinism has been treated by various methods. The frequent feeding of carbohydrate did not seem logical for by this procedure the insulogenic apparatus is constantly stimulated to produce more and more insulin. As a matter of fact, this very principle has been utilized successfully in the treatment of diabetes by giving patients a higher carbohydrate diet in order to "train the pancreas" to produce more insulin. Even in the preinsulin era, in certain severe cases of diabetes, when the high blood-sugar level could not be reduced on a prolonged low-carbohydrate diet, I used to turn about and give them a high-carbohydrate diet for a time and their blood sugar would drop like magic. I utilized this principle quite frequently but I did not know "how it worked" at the time. Only years later I found the explanation.

The low-carbohydrate, high-fat diet, I think, is a more logical procedure in the treatment of hyperinsulinism, for thereby one does not stimulate the pancreas to insulin production with a large load of carbohydrate but the small quantity of carbohydrate gets into the circulation slowly. Never having tried this diet without insulin, I cannot speak of it from experience, but others who have tried it did not seem very enthusiastic about it.

The operative procedure, with the exception of cases in which there is adenoma of the pancreas, does not seem a logical solution of the problem of hypoglycemia. If the kidney is removed and the other kidney is healthy, it hypertrophies and takes on the work of the excised kidney. No doubt the remain-

HYPERTENSION

History

THE past few years have witnessed an increasing incidence of a condition which, for lack of a more specific term, has been called "hypertension." There were always hypertensive cases, but as their complaints and the course of the disease were rectified, physicians began to wonder, after many years, what the condition really was. They had little or nothing to offer by way of treatment until the discovery of insulin and the subsequent work on blood-sugar studies which led to the discovery of insulinism. Estimations of the blood-sugar level were explained of intense hunger, nervousness, and occasionally unconsciousness. These symptoms appeared half hours after a meal and were relieved by a natural conclusion. The symptoms were the same as those of insulinism. Patients, however, did not want insulin for they disliked the treatment. They wanted carbohydrate in some form or other, but they did not want it less severe. They did not want to be treated or rendered it they wanted to be cured. They did not want to be cured because they had already been cured. They wanted a cure for this condition. It was not until these patients were at those times that the condition could be accounted for in one of two ways. First, too much insulin was secreted into the blood stream. Second, there was some interference in the nervous system of the insulogenic apparatus, which, when excited, could not be inhibited at the right moment. The resulting insulin until a marked degree of hypoglycemia was reached, was accompanied by symptoms. This explains why these symptoms were so frequent for the first few years both adults and children also

symptoms caused by an overdosage of insulin, had been diagnosed as a patient with early hyperthyroidism.

Fortunately, the incidence of hyperinsulinism is not so very great and the patients can be referred to specialists in this field of metabolism. Whether or not there will be a steady increase in this group, because of better understanding of this condition and a stimulated interest, only time will tell. In the last six months I have seen and treated six such patients.

The therapy of this condition has proceeded through a serial evolution of methods. The first was the frequent feeding of carbohydrate in an attempt to increase the level of the blood sugar. Next followed the use of the low-carbohydrate, high-fat diet which had its advocates. Then came the operative procedure of resection of a part (one-half to two-thirds) of the pancreas. The most recent method of treatment of hyperinsulinism with insulin injections is one which I have developed during the past few months.

If the pancreas can be trained to increase the production of endogenous insulin, could it also be trained to secrete less insulin? A brief review of biochemical changes in the blood stream in hyperinsulinism may help to answer the question. In the morning the patients have a low blood sugar. Following a meal, the level of the blood sugar rises and when it reaches a certain height, this postprandial hyperglycemia stimulates the pancreas to pour out insulin into the blood stream and the blood sugar begins to drop. Normally, the blood sugar reaches a certain level below 120 mg. per cent at which the insulin supply is automatically decreased or discontinued; in patients with hyperinsulinism, however, this regulation does not take place, and the blood sugar continues to fall to a very low level when the symptoms of hypoglycemic shock (insulin reaction) appear. This process repeats itself after each meal.

Thus the *upper level* of the blood-sugar curve represents the point at which the islands of the pancreas are stimulated to produce insulin and the *lower level* is the point at which the insulin reaction ensues because of the superfluous insulin in the blood and the consequent hypoglycemia.

ing portion of a partially removed pancreas undergoes similar work hypertrophy. In case of an adenoma of the pancreas, however, operation is the only logical procedure.

Within the past year, I have developed a new procedure for the treatment of hyperinsulinism with insulin. Superficially, this seems a wild statement, but it is a procedure which has produced amazing results in my hands and I am anxious to see others try it and to have a general clinical evaluation of the method. At the present time, the method is in the experimental state. Enthusiasm for its accomplishments must be tempered with reserve.

The rationale for the procedure follows: In the condition which is called hyperinsulinism, and by that I mean the group of symptoms of hunger, nervousness, palpitation, sweating and unconsciousness, there are several possibilities: (1) Quantitative increase in the insulin secretion, (2) disturbance in the nervous regulatory control of insulin secretion, (3) a tumor, an adenoma of the island tissue which results in increased secretion of insulin, or, as has been pointed out by some writers, the secretion of the adenoma, itself not insulin, may stimulate the islands to overproduction of insulin, (4) hypertrophy of the islands, and (5) continued overdose of insulin by injection.

I do not know of any way to differentiate the first and the second types. In the third type, the symptoms are usually more and more intense, the patient dies, and the presence of an adenoma is confirmed at necropsy by the pathologist. Wilder *et al.*¹ described in great detail one such case and I refer you to their original article. The fourth type I saw and described² two years ago when an old man, a physician, within a period of one and a half years went from marked insulogenic insufficiency (diabetes) which required 30 units of insulin per day (blood sugar 330 at beginning) into a marked insulogenic overabundance which was producing hypoglycemia with all its classic symptoms. At the postmortem examination, this change was explained by the presence of marked hypertrophy of the islands. The fifth type I described³ because I wanted to call it to the attention of surgeons because that particular patient with

100 systolic, 90 diastolic, the basal metabolic rate was minus 9 per cent, and the Wassermann test was negative. There was no glycosuria and the blood sugar was 84 mg. per cent one hour after a meal. A glucose tolerance test was done the next day which gave a diabetic curve. The condition was recognized as hyperinsulinism, although the evidence of decreased sugar tolerance somewhat complicated the picture. The patient was advised to increase the carbohydrate intake, with feedings between meals, and to return later for further observation.

She did not return for a year and four months, when she complained of the same symptoms, but they had increased in severity so that she was unable to carry on, even to do her housework. She had lost 4 pounds. It was at this visit that she was first referred to me.

A check of the blood sugar showed 74 mg. at noon and 56 mg. in the evening. The glucose tolerance test was repeated two days later, and yielded normal results. She was hospitalized for a few days on a diet of 100 Gm. of carbohydrate, 80 Gm. of protein and 253 Gm. of fat, a total of 3000 calories. With this she was given 10 units of insulin three times a day immediately after meals. She experienced no reaction while in the hospital and since her return home has had none, except once, when, for some reason, she took the insulin before a meal. After five days' treatment in the hospital, she was discharged and was advised to follow the same regimen at home.

Since her discharge from the hospital I saw her four times and more recently, I have had periodic reports through the mail which indicate a continued well-being and ability to partake of any and all activities, as had been her custom when she was in perfect health.

DISCUSSION

The results in this case have been very interesting to me and I begin to feel that a certain goal has been reached. After three months all insulin injections were discontinued at once and the patient kept on feeling well and having no reaction. Was the pancreas actually trained to put out less insulin or did something else take place? She gained 23 pounds which brought her

By giving insulin (10 units) to such a patient three times a day, half an hour after each meal, I reasoned that the following might be accomplished: A half hour (or less) after a meal the blood sugar has not yet reached the *upper level* of stimulation of the islands and the injected insulin should prevent its reaching this level. With the exogenous insulin in the blood stream, hyperglycemia fails to develop and there is no stimulation for the excessive output of endogenous insulin, which in the untreated patient causes the *lower level* of shock to be reached. If the dosage is properly adjusted (and the patient is not getting insulin from his pancreas) then the drop of his blood sugar should not reach the *lower level* at which the insulin reaction becomes manifest. In this manner, then, the patient's blood-sugar level is kept between the *upper* and the *lower levels*, the pancreas is placed at physiologic rest and hypoglycemia is eliminated.

Theoretically, such a pancreas, put at artificial rest over a period of time, should respond by a lesser output of insulin and the patient should be symptom-free. This, then, was the theory and I proceeded to find out whether or not it would work in practice. It did work marvelously. On February 23, 1933, this treatment was first tried on a patient with hyperinsulinism. In connection with the insulin injections a diet moderately high in fat content and with 100 to 140 Gm. of carbohydrate, 60 to 80 Gm. of protein and a total of 2500 to 3500 calories was used.

Case Report.—The patient was a woman, aged twenty-four, who first came to the clinic on November 10, 1930, complaining of fainting attacks. These attacks often lasted an hour, but taking food, especially sugar and orange juice, relieved these symptoms. She had been quite well until the birth of her child five years before. Her family history was unimportant, except that her maternal grandmother had had diabetes. The patient had had measles, chickenpox, tonsillitis, rheumatism and influenza, and had had a tonsillectomy at the age of eleven years. She had weighed as much as 124 pounds, but her weight on admission was 113 pounds.

Clinical examination showed that the blood pressure was

weight to normal and gradually she was able to change from the relatively high-fat diet to a normal diet and still all was and is well, for over seven months.

Whatever happened, the fact remains that the patient, since the first insulin injection, had no more reactions and began to improve; the improvement continued until a normal state of health was reached. A glance at the curve showing the results of the blood studies, however, shows that in general the level of the blood sugar was not raised. In fact, some of the recent blood-sugar checks show that the level was lower (24 mg. per cent at 12 noon without insulin) than it ever has been, and yet she has had no reaction, even at such times.

I am unable to venture any explanation, but merely to state the facts. Something happens within the human body, which at present we do not understand, which apparently adjusts the intricate mechanism to its proper function. The theoretical reasoning of trying to "train the pancreas to produce less insulin" led to a successful therapeutic result with apparent cure, but just how this happened still remains clouded in obscurity.

The results in the other 5 cases were similar but these patients have not been observed for so long a period of time as the first patient here described. It would be unnecessary repetition to describe them in detail, for the principle of the treatment which is new and of interest is the same in all the cases in this group.

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The first group of charts shows the course of the diabetes in children.

Case I.—A boy developed diabetes in 1927 when he was two and a half years of age and at that time his blood sugar

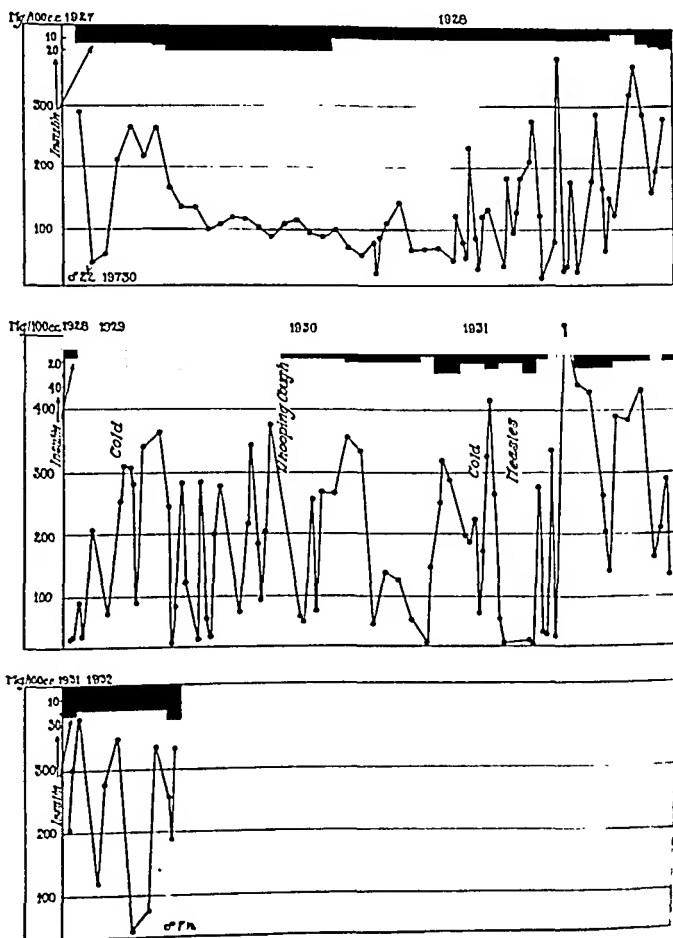


Fig. 173.—The case of a boy two and one-half years of age, followed over a period of five years. Note the slight increase of insulin with the advance of time and the high blood sugar excursions.

was 280 mg. per cent. Pneumonia is the only infection which preceded the onset of diabetes. His chart shows that for several months the disease was adequately controlled on a 1200-calorie diet and small dosage of insulin. Various infections be-

DIABETES IN CHILDREN AND IN ADULTS PAST THE AGE OF FIFTY YEARS

HENRY J. JOHN

ONE of the natural questions in considering diabetes as a whole is: Does diabetes differ in the young from diabetes which begins during the later decades of life? Is it more progressive in the young or is it as easily controlled in youth as it is in old age? Are there definite variations in the reactions of the two groups of patients? Do infections work as great havoc in the elderly diabetic patient as they do in the young? Do both types of patients experience decreased sugar tolerance and if so, is such a change a permanent one or is it merely a transitory change or is it one thing in children and another in adults? Should the young patient be given relatively more insulin than the old diabetic? These are all practical questions which confront every practitioner who deals with diabetes.

I can show you the answers to some of these questions by demonstrating some charts showing the clinical course in cases in the two groups. These show the ups and downs of these patients over a period of years. The blood-sugar determinations which are presented are usually made three times a day (before each meal), and the charts depict the excursions of the blood-sugar level. This procedure has been a routine part of my practice for several years, as I feel that only in this way can the insulin dosage be adjusted intelligently. This method shows just what each dose is accomplishing in the control of the patient's hyperglycemia and it enables one to make intelligent changes in the amount of insulin and at the proper time, in the morning, noon or evening dose. While the patient is in the hospital a twenty-four-hour sugar determination is made on the patient's urine which gives a further clue as to the efficiency of the patient's metabolic function. This would also be of great help if it were practicable to carry it out in the case of ambulatory patients, but, unfortunately, it usually is not possible since such patients stay in the hospital only from 8 A. M. to 5 P. M.

small dosage. For two and a half years this very small dosage was adequate. But during the latter part of 1931, the insulin had to be increased because the boy began to break his diet, a problem which always begins about the time a child starts to school. Today, then, his insulin requirements are growing because of infections and dietary indiscretions.

Case III.—A boy, five years of age, developed diabetes nine years ago and presented himself in a very emaciated condition,

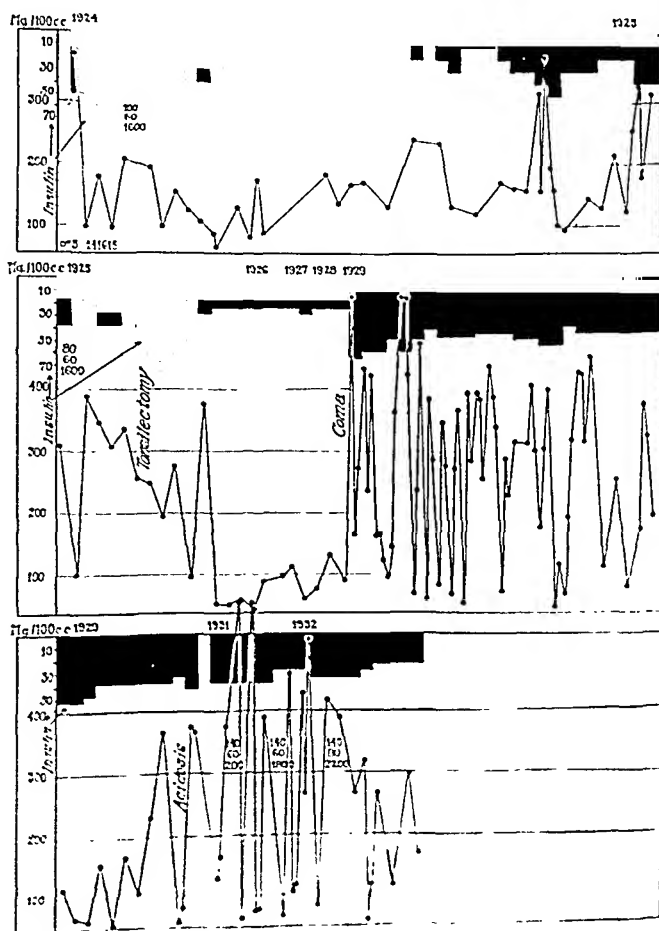


Fig. 175.—A boy, five years of age, who developed diabetes in 1924, followed over a period of nine years. The past two years his insulin requirement has diminished slightly.

gan to aggravate his condition and his insulin requirement has grown steadily with years. Besides, the blood sugar level varies widely. It is high in the morning and suddenly drops following the administration of insulin.

Case II.—A little boy, aged four years, developed diabetes in 1927, as did the first boy. A few months before the diabetes

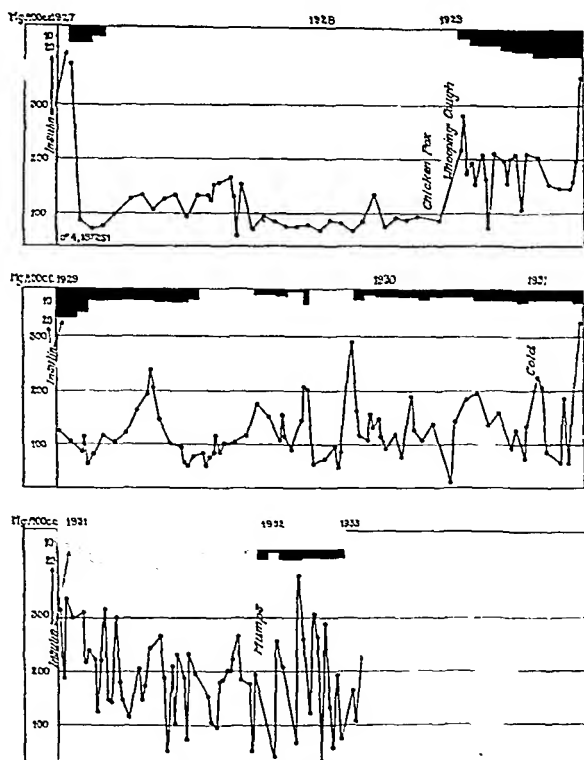


Fig. 174.—A boy who developed diabetes at the age of fourteen, followed over a period of five years. His insulin for the past two years had to be increased.

developed, he had measles and influenza and his initial blood sugar was 376 mg. For nearly two years he got along well without insulin. Then following chickenpox and whooping cough, the blood sugar rose and he had to have small doses of insulin. After a few months, insulin again was discontinued but some months later had to be resorted to temporarily in very

had a blood sugar of 490 mg. Her diabetes followed the onset of grippe. Under treatment, the blood sugar descended rather rapidly and when she left the hospital, she needed only a small dosage of insulin. The insulin requirement grew, especially following measles, and for the last five years she has had to have rather large doses of insulin.

Case V.—In a boy, twelve years of age, when he was first seen in 1930, the onset of diabetes followed shortly after a frac-

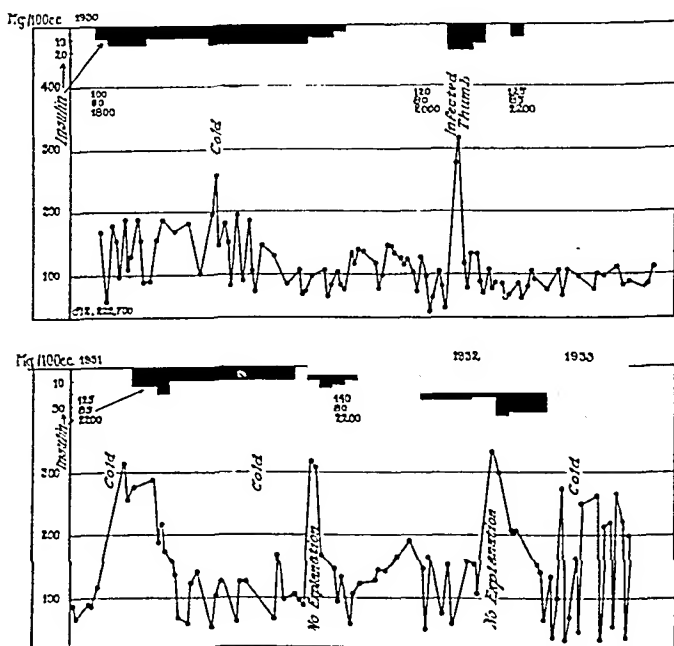


Fig. 177.—A boy, twelve years of age, who developed diabetes in 1930. This child has been under very close supervision, still his insulin requirement is rising.

ture of the clavicle. His blood sugar then was 167 mg. He made steady progress for over a year until an infection supervened in 1931. This boy has been under extremely close supervision and has done well on the whole, yet his insulin requirement is constantly increasing. There are also sporadic extreme

with a blood sugar of 386 mg. Swollen cervical glands preceded the onset of diabetes. His insulin requirement dropped rather promptly until he developed tonsillitis four months later when the insulin requirement was increased. Following tonsillectomy, the blood sugar dropped as did the need for insulin and the blood sugar stayed at the normal level for over three years. The onset of coma in 1929 changed the picture, for following this his need for insulin stayed high for a month when the dose could again be reduced. Acidosis developed again seven months later and after that I did not see him for two years. During the last two years, however, his insulin requirements have been diminishing slightly.

Case IV.—A girl, ten years of age, when she was seen first seven years ago only a few days after glycosuria developed,

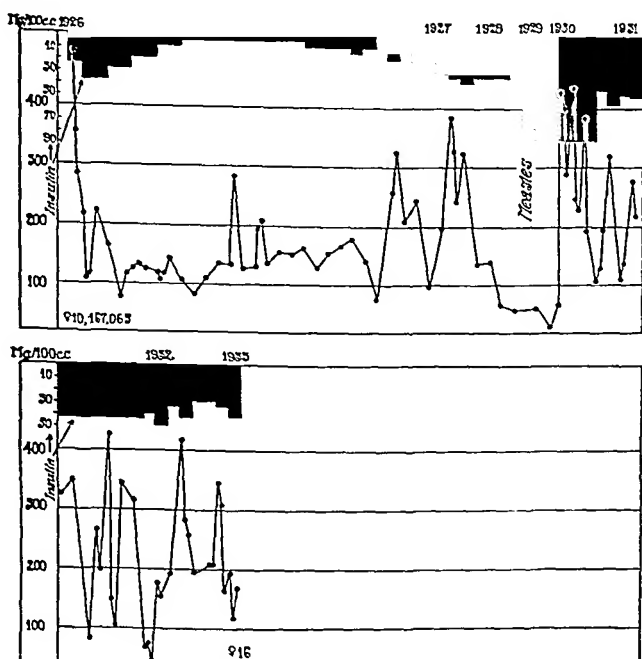


Fig. 176.—A girl, ten years of age, who developed diabetes in 1926, followed over a period of seven years. Note the increased insulin following measles.

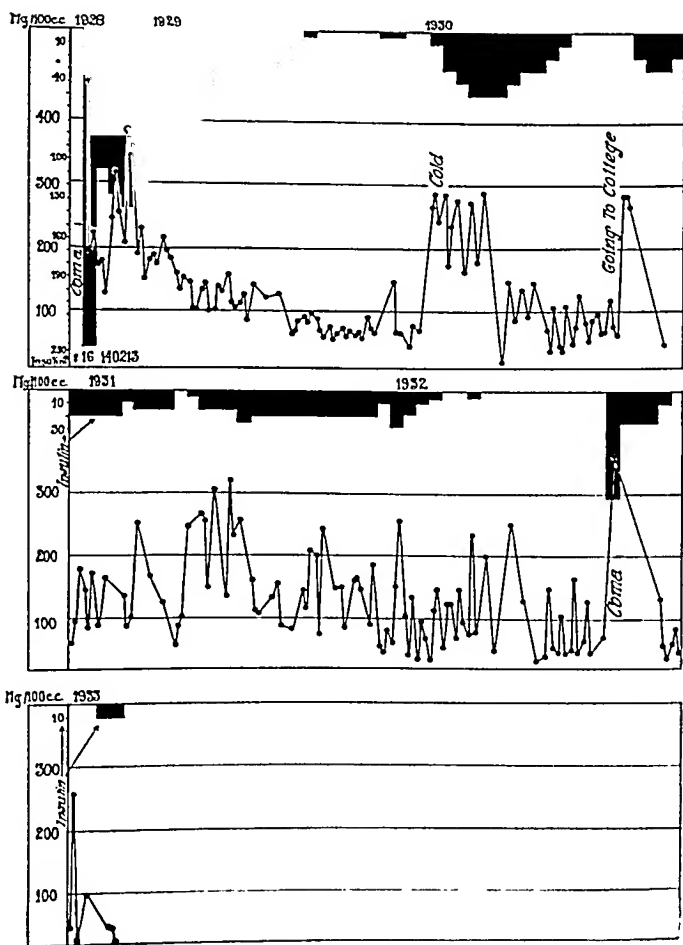


Fig. 179.—A girl, sixteen years of age, whose diabetes was first discovered five years ago, when she was in coma. She has a mild case and is able to go without insulin for long intervals of time.

Case VIII.—This boy was seventeen years of age when he developed diabetes six years ago, but he had had some glycosuria at the age of fourteen years. No predisposing cause for the diabetes could be elicited. His progress for a year has been good. But as in the other cases, infections have aggravated his condition and insulin has had to be resumed from time to time.

risers of blood sugar which show up on routine examinations and which I have not been able to explain.

Case VI.—This patient's diabetes was first discovered when he was at a camp in another state, six years ago. At that time he was aged fourteen. He has done well on treatment, is now in college, but his insulin requirement is rather stationary. He just returned from a trip to Europe, which shows that an intelligent diabetic can take care of himself well.

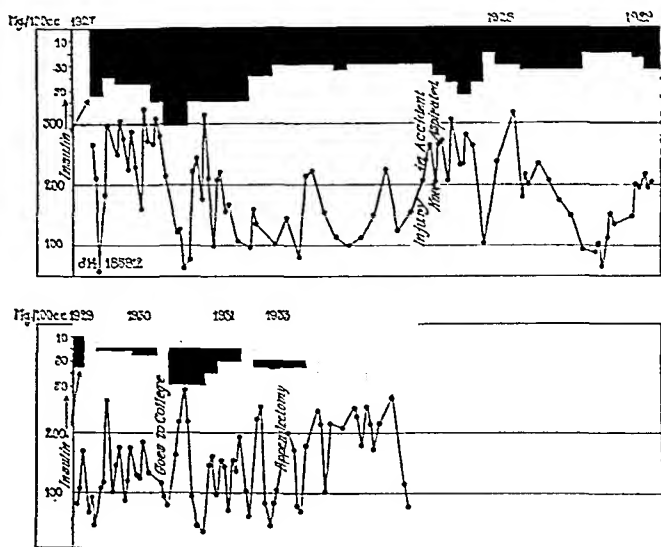


Fig. 178.—A boy, fourteen years of age, followed over a period of six years. His insulin requirement is stationary.

Case VII.—A girl developed diabetes five years ago when she was sixteen years of age. In fact she was in coma at the time when the disease was diagnosed and at no time previously had she had any symptoms referable to diabetes. She had intestinal influenza and within twenty-four or twenty-eight hours she was in coma. The chart shows that her insulin requirement is diminishing for there are long periods when she gets none. Still, an infection precipitates a rise of blood sugar and insulin has to be reinstated.

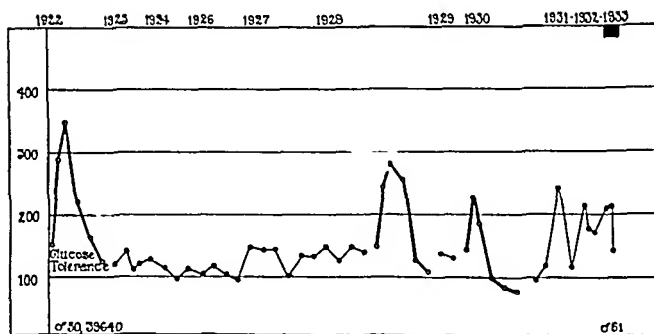


Fig. 181.—A man, fifty years of age, followed over a period of eleven years. Note the borderline diabetic condition fluctuating up and down.

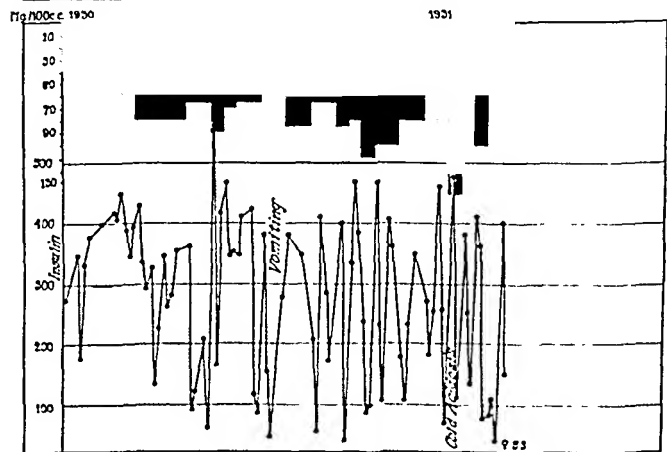
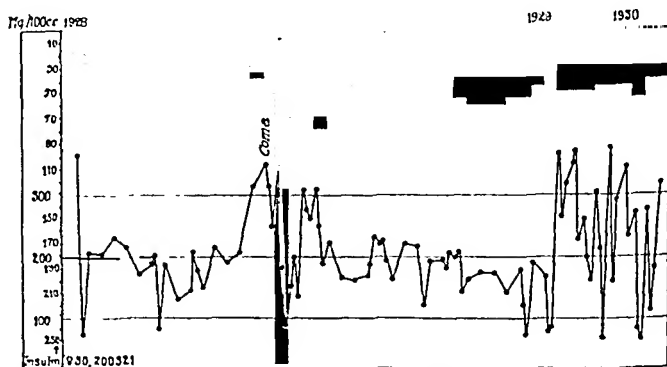


Fig. 182.—A woman, fifty years of age, followed over a period of five years. A mild diabetic condition at the start, growing progressively more severe.

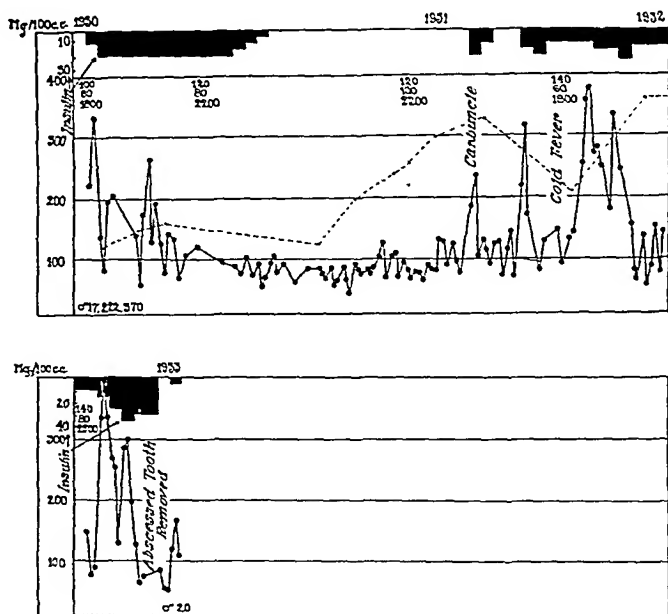


Fig. 180.—A boy, seventeen years of age, followed over a period of three years. A mild case of diabetes, going without insulin for long intervals of time, but having to resume the use of insulin periodically.

Of the eight children here presented, six are taking more insulin as time goes on, the condition of one is stationary and one has had a decrease in the required amount of insulin. These cases show the progressiveness of diabetes in the young, for these cases are not selected cases but taken from a large series. A problem which is still unanswered is: Will this insulin requirement keep on increasing or will it finally reach a stationary level and then decrease as the patients mature?

Case IX.—A business man, aged fifty years, whose father had died of diabetes at a very advanced age, consulted me eleven years ago. A glucose tolerance test was done to see whether or not there was any abnormality in his carbohydrate metabolism. The chart shows that the curve was mildly diabetic. After that, he exercised great care in his diet and over a period of years only a slight hyperglycemia was manifest. The glucose tolerance test was repeated six and eight years later, and showed steady improvement. I do not know whether it was

sugar was 386 mg. This dropped promptly and in eleven days it was possible to discontinue all insulin for several years. Only during the past year has she been taking small doses of insulin on account of a slight rise in her blood-sugar level.

Case XII.—This chart shows the course of the disease in a man who was fifty-four years of age when a mild diabetic condition was diagnosed ten years ago. With slight fluctuations of blood sugar and insulin requirement, his present state after ten

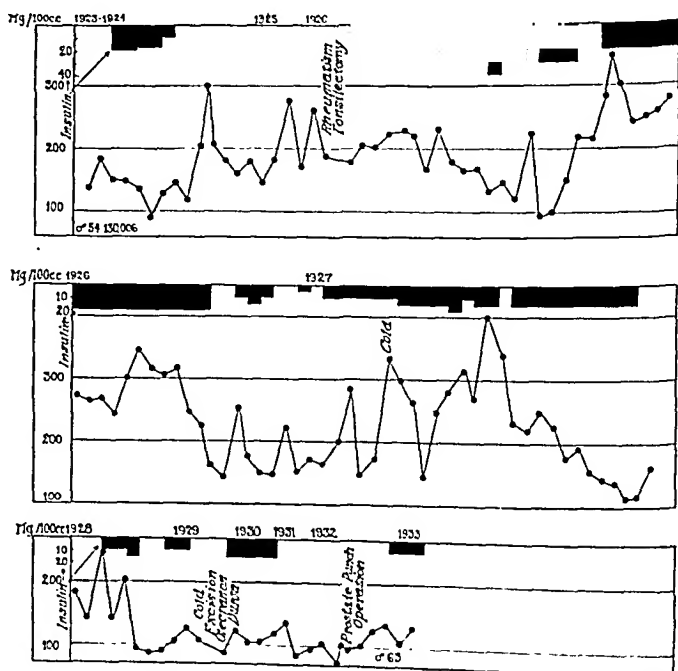


Fig. 184.—A man, fifty-four years of age, followed for ten years, showing a stationary diabetic condition.

years is such that he needs no insulin. However, he insists on taking insulin for it makes him feel much better. He says that now at the age of sixty-four years his mind is more clear and he has more energy when he is taking small doses of insulin.

Case XIII.—This patient, a woman, had had diabetes for twelve years. She was fifty-six years old when the disease began. For over two years the diabetes was controlled by diet

alone, later insulin was given. For a year (1930) she had no insulin and is getting none at present. Her chief problem is a

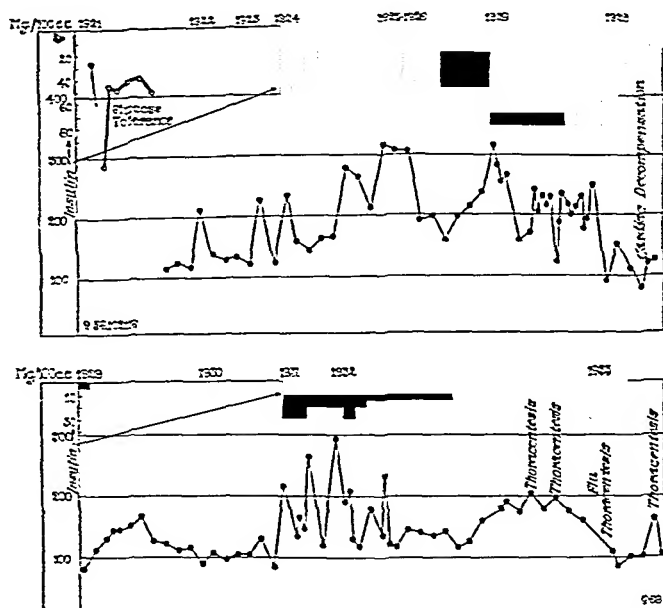


Fig. 185.—A woman, fifty-six years of age, followed for twelve years. Note the improvement of the diabetic condition over a period of time.

periodically decompensated heart. Her diabetic condition, on the whole, has improved with time.

Case XIV.—This man was fifty-eight years of age six years ago when he became diabetic. He has since had both legs amputated because of gangrene. During this entire time his insulin requirement has been stationary and from present indications it may be possible to decrease it (Fig. 186).

Case XV.—This woman, now seventy years of age, has been diabetic for ten years. During this time she has had a gangrenous toe amputated and in 1930 had a fractured hip. Her diabetic condition has been mild throughout its entire course, and her insulin requirement is diminishing despite the fact that her diet is not closely controlled (Fig. 187).

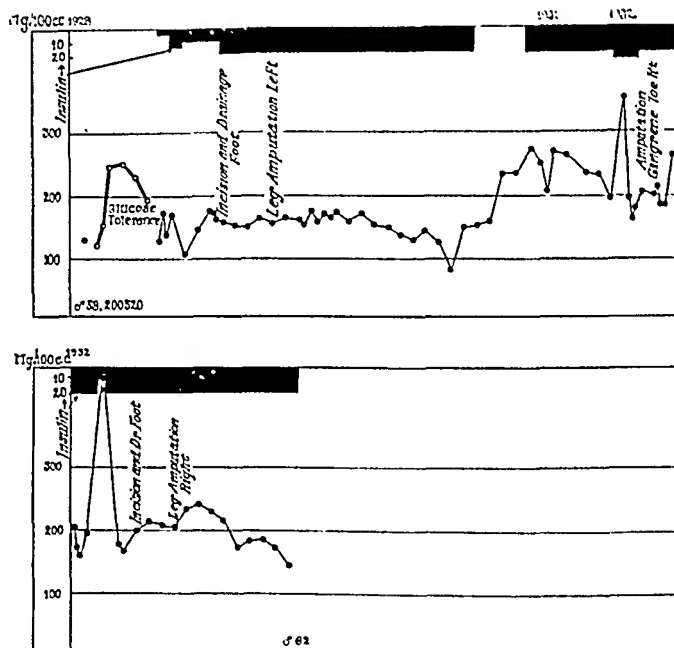


Fig. 186.—A man, fifty-eight years of age, followed for five years. During that time he had both legs amputated but his diabetic condition is stationary.

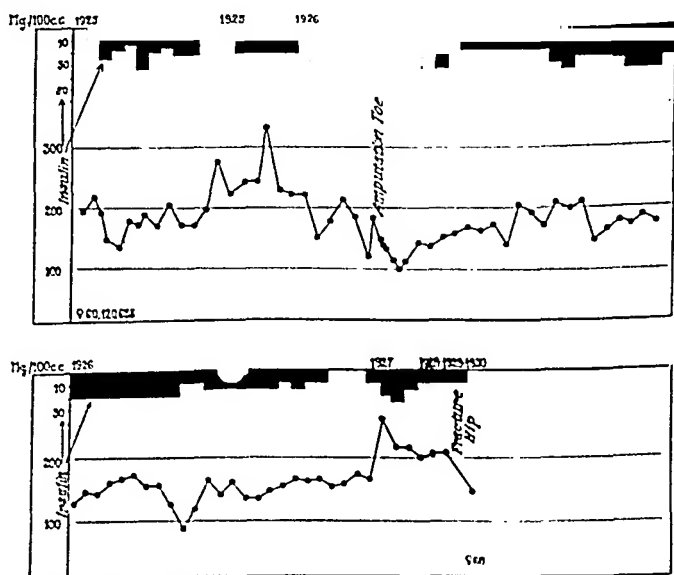


Fig. 187.—A woman, sixty years of age, followed for ten years. She has mild diabetes with a decreased insulin requirement.

Case XVI.—This patient, a man, was sixty-two years of age when he became diabetic nine years ago. During this time he has had both legs amputated because of gangrene. The dia-

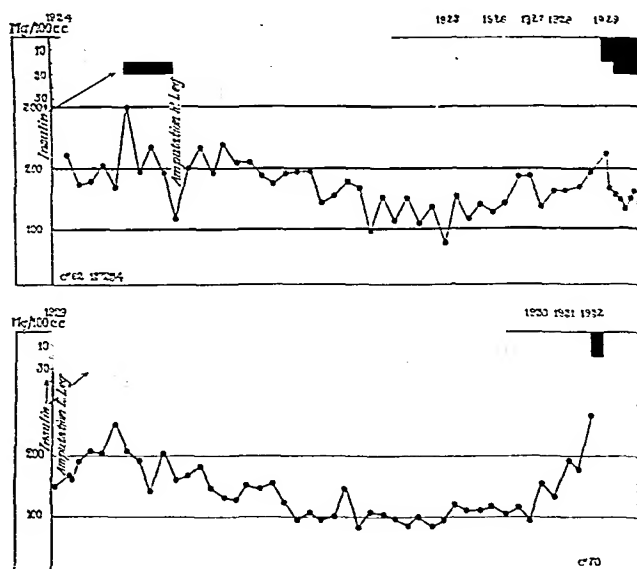


Fig. 188.—A man, sixty-two years of age, followed for nine years. Both legs were amputated during this time. Note the decreased requirement of insulin as time progresses.

betes began mildly and during two intervals he had no insulin for a period of years. His condition still is not severe and only recently has a small dosage of insulin been prescribed.

Case XVII.—This patient, like the one just described, is now seventy-one and he has had diabetes for seven years. His blood sugar was 400 mg. at first and he was given insulin for nine days, but after that he went without insulin for three years until he developed an infection, cystitis, when again insulin had to be reinstated. However, for nearly three years, he has had no insulin and the blood sugar is normal (Fig. 189).

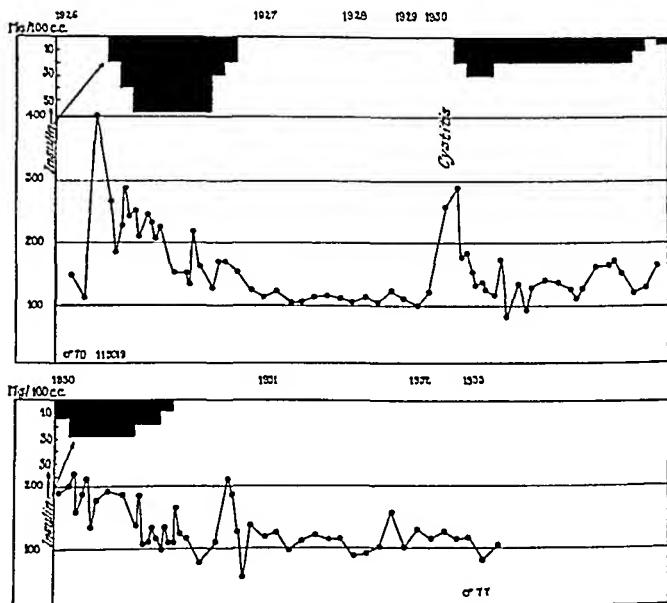


Fig. 189.—A man, seventy years of age, followed for seven years. Note the effect of infection even in a mild case of diabetes. With time his diabetic condition has been progressively milder.

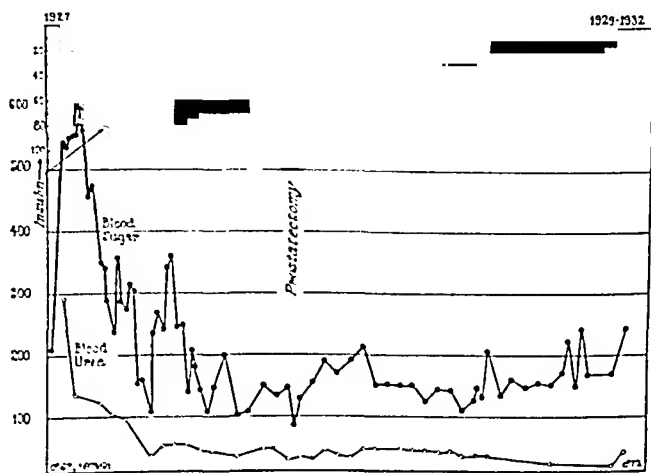


Fig. 190.—A man, sixty-seven years of age, followed for six years. He was in coma when admitted (diabetic acidosis and nephritic coma). He had a major operation, and today, six years later, at the age of seventy-three years, he is still carrying on a busy country practice.

Case XVI.—This patient, a man, was sixty-two years of age when he became diabetic nine years ago. During this time he has had both legs amputated because of gangrene. The dia-

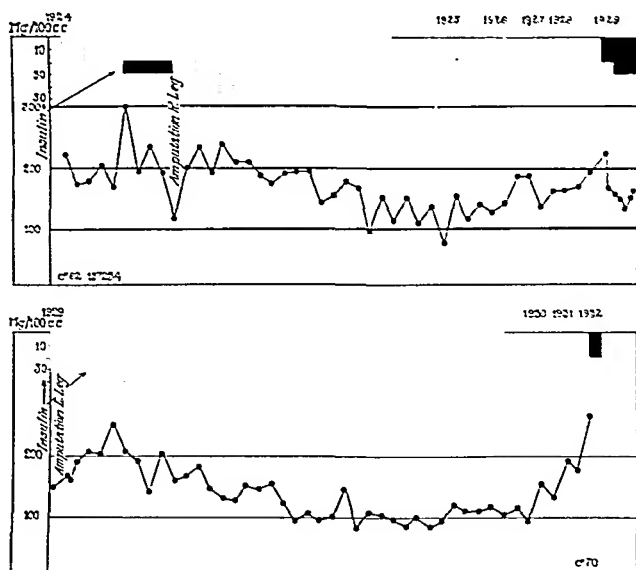


Fig. 188.—A man, sixty-two years of age, followed for nine years. Both legs were amputated during this time. Note the decreased requirement of insulin as time progresses.

betes began mildly and during two intervals he had no insulin for a period of years. His condition still is not severe and only recently has a small dosage of insulin been prescribed.

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stress they are likely to die or to lose some of their sugar tolerance. Even the old diabetic, though slowly progressive, needs close supervision although this need not be so rigid as in the group of young patients.

In children, infection is the chief enemy. In twenty-four hours a child, even though but mildly diabetic and needing no insulin (as Case VII), can go into coma. Relatively the young diabetic patient requires more insulin than the older person. In patients in whom there are extreme blood-sugar fluctuations which cannot be controlled or stabilized with any amount of insulin, I feel that we must be dealing with deficiency in the storage of glycogen in the liver. This type of case presents the greatest difficulty in management. In children of this type we find at necropsy a fatty liver. As yet we do not know what the answer will be as to the status of these youthful diabetics twenty or thirty years from now, but the prospects seem quite promising. The diabetic child today is taking his place in the world, and offers us an opportunity to study the evolution and the progress of the disease. By observing such a patient over a long period of years we should be able to learn many new things. The insulin era is still in its infancy and thus far we have but laid the foundation for future work and investigations in diabetes.

Case XVIII.—This patient became diabetic six years ago. He was first seen and his diabetes was controlled by insulin. His diabetic condition was controlled by insulin following which his insulin requirement was reduced to a dosage and today at the age of 65 years, he is well and hearty, still carrying on a busy life in his country (Fig. 190).

These charts tell the story of the contrasting features of the two groups.

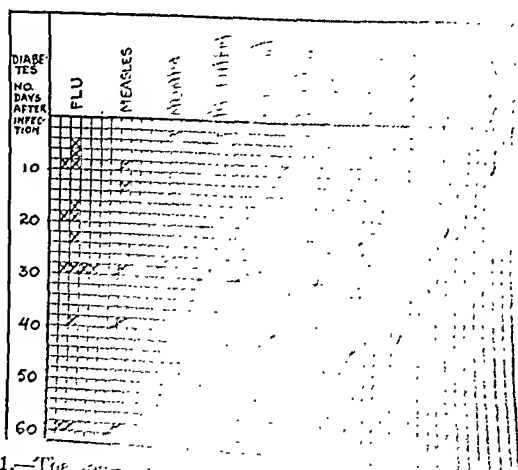


Fig. 191.—The same as Fig. 190, but showing the effect of the following

the onset of *schizophrenia*,
the various *symptoms* of *childhood* following
many of *these* *the* brevity of time

[illegible]

had never received antisyphilitic treatment. She had no signs of syphilis and the blood Wassermann and Kahn tests were negative.

On February 26, 1932, she was given 0.3 Gm. neosalvarsan; on March 1, 1932, 0.3 Gm., and on March 5, 1932, 0.6 Gm. There were no nitritoid reactions and the patient had no immediate symptoms. On March 7th at 11 A. M. she noticed that she was dizzy. She became restless and began to develop motor aphasia. She had also developed a mildly pruritic eruption on the chest and abdomen. She was seen at 5 P. M. and advised to enter the hospital. She had a mild erythematous dermatitis on the trunk, was irritable, the reflexes were hyperactive and there was definite aphasia. She did not complain of a headache at this time but was dizzy when in the erect position. One Gm. of sodium thiosulphate was given intravenously. At 9 P. M. she had a convulsion and became noisy, very restless, and irrational.

The patient was extremely restless and excitable; reflexes were hyperactive; pupils were dilated and there was a bilateral Babinski reflex. She kept her arms and legs moving almost continuously. She was semiconscious and complained of a severe headache. Her temperature was 100.6 F. One cc. of adrenalin and 500 cc. of a 25 per cent solution of glucose were given. Two hundred cc. of 25 per cent glucose were given twice a day for four days and after that once a day until her symptoms disappeared.

The second day the temperature was 100.8 F. A spinal puncture was done. The fluid pressure was 125 mm.; the fluid was clear but slightly yellow. The laboratory report was 2 cells per cubic centimeter. The Wassermann reaction was negative; the colloidal gold reaction was 1122222100. The fluid contained a trace of globulin. The urine showed a trace of albumin. She was not so restless or irrational but vomited frequently and voided involuntarily. She continued to receive adrenalin, 1 cc. every two hours, and was given 200 cc. of 25 per cent glucose intravenously and a second injection of 1 Gm. of sodium thiosulphate. One Gm. of magnesium sulphate and $\frac{1}{4}$ grain morphine were given intramuscularly as a sedative.

HEMORRHAGIC ENCEPHALITIS (SEROUS APOPLEXY) FOLLOWING THE ADMINISTRATION OF NEOSALVAR- SAN. REPORT OF TWO CASES WITH RECOVERY

E. W. NETHERTON

ONE of the most serious complications in modern antisyphilitic therapy is encephalitis or serous apoplexy. It is produced only by the arsphenamines and is considered to be a manifestation of intolerance to arsenic. Sulpharsphenamine seems to be the arsenical most likely to produce this very alarming condition. Fortunately this type of encephalitis is very rare; but if it occurs the prognosis is grave, for the patient usually dies within a comparatively short time. The outlook for recovery depends a great deal upon promptness in institution of the energetic treatment after the onset of symptoms. Some observers have felt that this complication was of the nature of a Herxheimer reaction; however, most authorities consider it to be an arsenical intoxication, the nature of which will be discussed later. Most of the recorded cases have occurred in syphilitic patients, but with the increasing frequency with which the arsphenamines, notably neoarsphenamine, are being used for their nonspecific effect, as in cases of arthritis, erythema induratum, Vincent's infections, etc., no doubt cases will be observed more frequently in nonsyphilitic persons.

I have observed two patients with encephalitis resulting from the administration of neoarsphenamine, both of whom recovered. One was a patient with hereditary syphilis while the other was treated for a resistant Vincent's infection.

Case I.—A divorcee, aged thirty-two, with a negative past history was referred to me for treatment with neosalvarsan because of Vincent's angina. She also had arthritis of the left sacro-iliac joint. She denied having had a venereal disease and

severe headache. She soon became nauseated and vomited and in a few hours began to have fecal incontinence. She was very restless, all reflexes were hyperactive. There was a Babinski reflex on the right side and an impairment of the left abdominal reflexes. Pupils were equal and regular and reacted to light and accommodation. There was no nystagmus. The neck was not stiff, yet her head was held extended.

A lumbar puncture was done soon after she was admitted. Because of the struggling of the patient it was impossible to measure the spinal fluid pressure. The fluid findings were as follows: Clear; 2 cells per cubic centimeter; trace of globulin (Pandy); total protein 70 mg. per hundred cubic centimeters, and sugar 75 mg. per cent. The Wassermann and Kahn tests were negative, and the colloidal gold was 4433321000. The urine showed a faint trace of albumin. Blood counts showed 5,050,000 red blood cells, 12,000 white blood cells and a differential count of 79 per cent; polymorphonuclear neutrophils, 14 per cent, lymphocytes, 30 per cent, eosinophils, 1 per cent, and mononuclears, 4 per cent.

A diagnosis of encephalitis following neosalvarsan was made. Adrenalin, 2 cc., was given hypodermically and 500 cc. of 25 per cent solution of glucose were administered intravenously. The adrenalin was repeated in 1-cc. doses every two hours. She was also given 0.6 Gm. of sodium thiosulphate intravenously.

The next day the patient was irrational, constantly moving her extremities and frequently crying or screaming because of a severe headache. The rectal temperature was 103.2 F. and the pulse rate 140. Glucose, 125 cc. of a 25 per cent solution, was given intravenously night and morning.

The following day some improvement was noted but the patient was extremely irritable when any treatment was attempted and had involuntary micturition. Adrenalin and glucose were continued and 1 Gm. of sodium thiosulphate was given intravenously. The rectal temperature was 102.2 F.

The third day after her admission to the hospital, there was marked improvement. She was quiet and rational but hyper-

Improvement was gradual. Her hyperactivity and stupor had almost disappeared on March 15th, the seventh day in the hospital. Adrenalin and hypertonic glucose were then discontinued and she was discharged from the hospital on March 18th, apparently recovered from her acute illness. About a month later her physician gave her some sodium cacodylate for arthritis. In a few hours she became dizzy and developed a slight erythematous eruption over the body. She stated that her symptoms were similar to those she experienced at the onset of the illness which was produced with neosalvarsan.

Case II.—A girl, thirteen years of age, suffering from congenital syphilis, was first examined on January 2, 1932. Both parents had strongly positive Wassermann reactions. The father had the meningovascular type of central nervous system syphilis.

The patient was well developed, being large for her age, and of average mentality but had always been restless. The only signs of congenital syphilis were Hutchinson's teeth, 4 plus blood Wassermann and 4 plus Kahn reactions. Her past illnesses had been measles, mumps, and chickenpox. The mother was sure there had been no manifestations of the infection in infancy. She had not received antisyphilitic therapy.

On January 16, 1932, antisyphilitic treatment was started with potassium iodide by mouth and a soluble bismuth intramuscularly twice a week. After ten injections of bismuth, neosalvarsan was started. On February 23rd she received 0.2 Gm.; on February 27th, 0.3 Gm.; March 5th, 0.45 Gm.; and on March 12th, 0.45 Gm. There were no nitritoid or other reactions following any of these treatments. On March 16th, the fourth morning following her last neosalvarsan injection, she complained of a mild headache, but it was not severe enough to prevent her from attending school. About five o'clock in the afternoon, while practicing on the piano, she fell to the floor, became confused, and had a generalized convulsion. It was with difficulty that she was aroused after the convulsion. She was admitted to the hospital four hours later, at which time she was noisy, tossed about continuously and complained of a

frequent intervals and the patient becomes comatose or delirious. There is hyperkinesia, the patient constantly moving the arms and legs or tossing about the bed. The face may be flushed or cyanotic. Vomiting accompanied by fecal and urinary incontinence may occur shortly after the onset of symptoms. The reflexes are hyperactive, the pupils are usually dilated and a Babinski sign is usually present. Occasionally a Kernig sign may be elicited. The condition of the patient rapidly becomes worse and death usually occurs within forty-eight hours. The terminal high temperature and rapid, feeble pulse may be accompanied by Cheyne-Stokes respiration.

There is a slight leukocytosis and occasionally mild albuminuria. The spinal fluid is essentially negative. This is of importance in differentiating acute syphilitic meningitis and neurorecurrence from this type of encephalitis.

Several theories regarding the etiology of this complication have been advanced. Attempts have been made to show that the fault lies with the drug, and that it is the result of chemical deterioration, overdosage, or an error in the technic of preparation and administration. Since isolated cases have developed in groups of individuals who received injections from the same lot or mixture of salvarsan it is apparent that this explanation is inadequate. The dosage of arsphenamine, although important in the proper management of syphilis, cannot be of major significance as a cause of encephalitis as this complication frequently follows the injection of small amounts of the drug. The opinion expressed by Gjessing² and others, that the syphilitic infection is a factor, may be disregarded, as encephalitis has been observed following the administration of the arsphenamine to nonsyphilitic individuals, as in the first case herein reported. Lasersohn³ and others have recorded similar cases. These observations discredit the theory that the liberation of endotoxins following the dissolution of the spirochetes is a factor in the causation of this form of encephalitis. Milian,⁴ in discussing the report of Gjessing, discredited the importance of syphilis as a factor in the causation of this condition. On the other hand, these observations suggest that the drug is at fault.

excitable when disturbed. Adrenalin and glucose were continued.

The following day she was completely oriented and all symptoms had disappeared except for some irritability. She continued to improve rapidly and was discharged from the hospital on the eighth day without any apparent ill effects from her acute illness. Four months later she was in as good a condition as when treatment was started.

Hemorrhagic encephalitis as a complication of antisyphilitic therapy is a product of the modern arsphenamine era. The complication, although rare, is responsible for a large proportion of arsphenamine deaths. Stokes¹ observed 1 case in 63,000 injections, while Cole and his associate noted 6 cases in approximately 78,350 injections of the various arsphenamines. The relatively large incidence in Cole's series may be explained by the fact that sulpharsphenamine, the most toxic of all the arsenicals, was the drug used in 4 of the 6 cases in which this complication developed. Although the incidence of this serious complication is small compared with the large number of injections of arsphenamine that are given, it is the most dreaded hazard of this type of therapy and the possibility of its occurrence should be kept in mind by those who administer this drug.

Encephalitis usually develops early in the course of treatment, frequently after the first, second or third injection. Symptoms are first noticed the second or third day after the last treatment, the patient having shown no evidence of intolerance to the drug at the time of its administration. This delay in the appearance of symptoms is unfortunate as treatment may not be instituted as soon as desirable. This is frequently the case when the symptoms appear insidiously.

The most alarming early symptom is a headache which may be accompanied by nervousness, apprehension and giddiness. These symptoms gradually increase and the patient becomes confused, disoriented, noisy, delirious and finally comatose. In other cases a convulsion followed by stupor simulating epilepsy may be the initial symptoms. The convulsions may occur at

served throughout the brain. The hemorrhages which occur as rings of extravasations around the capillaries and small blood vessels are most numerous in the pons, corpus callosum, and in the white substances of the cerebral hemispheres. The vessels are engorged and their endothelial lining is edematous. Thrombosis and areas of necrosis may develop. Although there may be some leukocytic infiltration, a marked inflammatory reaction does not occur.

Much depends upon an early and accurate diagnosis. Encephalitis caused by arsphenamine must be differentiated from acute encephalitis of the epidemic type, Herxheimer reaction, neurorecurrence, epilepsy, acute syphilitic meningitis, and acute disseminated syphilitic encephalitis. The diagnosis may be difficult and at times impossible if based entirely on clinical findings. This is especially true if the epidemic type of the disease is prevalent. If the patient has been given arsphenamine two or three days prior to the appearance of the illness it is best to assume that he is suffering from arsenical intoxication and start treatment as early as possible.

A Herxheimer reaction or therapeutic shock is the result of activation of a syphilitic process by the indiscrete administration of too large a dose of arsphenamine, without preparatory treatment with bismuth or mercury. It is seen most frequently in early syphilis. The accentuation of visible symptoms of syphilis and the development of localizing signs are valuable aids in the diagnosis. The symptoms of a Herxheimer reaction subside in a comparatively short time.

Neurorecurrence, a manifestation of activation of a syphilitic infection, occurring during inadequate arsphenamine treatment, may simulate encephalitis, especially if it is of the epileptiform type. The history of a recent syphilitic infection and the development of cranial nerve palsies, which is so common in this condition, are important differential points. In neurorecurrence there usually is a marked increase in the cell count of the spinal fluid and the serological tests give positive reactions. The patient is more acutely ill in encephalitis. It is important to differentiate these conditions for active arsphen-

The evidence favors the opinion that this type of encephalitis is the result of an idiosyncrasy of the affected individual to arsphenamine.

Decreased kidney function resulting from intensive mercurial medication and other causes, or cirrhosis of the liver, which interferes with the elimination and metabolism of the arsenicals, may contribute to the causation of this complication.

It is of interest that soon after arsphenamine encephalitis was recognized, Ehrlich expressed the opinion that the delay in the onset of symptoms indicates that a derivative of the salvarsan is the cause. He thought that it was an oxidation product, known as paraminophenyl-arsenoxide and that diminished kidney function favored the formation of this product. He also mentioned adrenalin insufficiency and the use of adrenalin in this condition.

Milian considers encephalitis developing after salvarsan injection as an angioneurotic syndrome analogous to the nitritoid reaction. He feels that adrenalin insufficiency resulting from injury to the sympathetic nervous system by the salvarsan or by disease is a contributing etiologic factor. This opinion is supported by the fact that adrenalin is of great value in the treatment of this condition and also by the observations of Gjessing who was able to continue with arsenical medication in a patient who had recovered from serous apoplexy, by the administration of adrenalin before injecting neosalvarsan.

It is obvious that we do not know why the arsphenamines cause hemorrhagic encephalitis. It is probable that it is the result of factors inherent in the individual, although impairment of function of the visceral organs with subsequent faulty excretion and metabolism of the drug may contribute to its causation. Their importance, as predisposing factors, becomes less evident when one considers that the incidence of arsphenamine encephalitis is small compared with the large number of patients with damaged viscera receiving this type of medication.

The pathologic findings revealed at autopsy are similar to those observed in other types of acute encephalitis. There is marked edema, and numerous petechial hemorrhages are ob-

arsphenamine. It should be given in large doses and at frequent intervals. One or 2 cc. is administered subcutaneously every two hours until improvement is noted. Oral administration of this drug is of no value.

McBride⁸ was probably the first to demonstrate the value of sodium thiosulphate in encephalitis caused by salvarsan. Lasersohn,³ Dickens,⁹ Sheppe,¹⁰ Dennie¹¹ and others also have found this drug of value in this condition.

Hypertonic salt solutions are of value as they reduce the cerebral edema. Five hundred cm. of 25 per cent solution of glucose should be given twice a day until the patient shows improvement. It is of value in case of accompanying liver damage and is preferable to salt solution.

Magnesium sulphate and morphine intramuscularly is a satisfactory sedative and should be used if the patient is delirious. Venesection, purgation, and the administration of oxygen are advocated by Fraser and Duncam¹² and Schamberg and Wright.¹³

We have no method of preventing this unfortunate and serious complication of arsphenamine therapy. Although there is no evidence which would indicate the probable development of encephalitis following salvarsan therapy, it is advisable to precede the administration of arsphenamine by an injection of adrenalin in cases showing intolerance to the drug, especially if the intolerance is manifested by nitritoid reactions. The value of this procedure is demonstrated in the case reported by Gjessing.

The two patients herein reported are of interest because they represent typical examples of this rare condition and because they recovered. Their recovery may be due to the fact that the cases were mild, but I am of the opinion that the prompt beginning of treatment soon after the onset of the symptoms contributed to the favorable outcome. The first case is of special interest in that it contributes additional evidence against the theory that the syphilitic infection is a factor in the causation of encephalitis following the administration of arsphenamine.

amine therapy is beneficial in neurorecurrence while in encephalitis it would be disastrous.

The history of previous convulsions and the absence of alarming neurological findings following the convulsion distinguish epilepsy from encephalitis.

Acute syphilitic meningitis may be excluded by evidence of cranial nerve involvement and the high cell count in the spinal fluid.

It is doubtful that acute disseminated encephalitis is ever produced by a syphilitic infection. Stokes⁶ cites a questionable case that he observed. In this case the symptoms were indistinguishable from those of arsphenamine encephalitis.

It may be impossible to differentiate arsphenamine encephalitis from all of the conditions mentioned above. In case of doubt the condition should be treated as encephalitis until subsequent observation establishes the correct diagnosis as the prognosis in this condition is dependent to a great extent upon the interval between the onset of symptoms and the institution of treatment.

It is not known how soon the hemorrhage in arsphenamine encephalitis occurs; however, there is evidence which suggests that it is preceded by edema, as a few cases in which an autopsy was done have shown marked edema and few hemorrhages. It is probable that the mortality in this type of arsenical intoxication might be decreased if vigorous treatment could be started in all cases early, at the time the pathologic condition is that of cerebral edema.

Treatment consists of large and frequent doses of adrenalin, sodium thiosulphate and intravenous injections of hypertonic solution of glucose or sodium chloride. A spinal puncture should be done provided there is no choking of the optic disks; for it is of therapeutic and diagnostic value.

If given early, adrenalin combats the vasodilator action of the arsphenamine. Its value in the treatment and prevention of nitritoid reactions is well known. Milian, Beeson,⁷ Stokes, and others advocate its use in these conditions and consider it the most important remedy for encephalitis caused by

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are necessary for clear, comfortable vision and failure or weakness in any system may cause general body discomfort.

Aside from their use in placing the head in better position for hearing or eating almost all neck movements are made to place the eyes in better seeing position, and it requires almost continuous head movement to maintain good comfortable vision. The major neck muscles involved are the trapezius, the capitus longus group, and the pair of sternocleidomastoids. The last two are primary in rotation of the head, and acting together, elevate the chin; the trapezii are also elevators of the chin and rotate the head. The insertion of these main groups of muscles along the superior and the inferior nuchal lines and at the tip of the mastoid process are important, for many patients localize their pain at these points.

Faulty eye-muscle balance causes the head to be fixed in position and results in hypertrophy of some muscles and relative atrophy of others. A study of the neck is important as to size, contour and development.

The field of vision would be tremendously lessened by inactivity of the neck muscles, as the arc of rotation for the muscles is vastly greater than that of the eye muscles acting alone. When the eyes are directed toward an object, the external eye muscles are brought into play. These muscles, six for each eye, do not act singly but as a unit. This unity of action of the external eye muscles must be maintained to assure comfortable use of the eyes. It is just as essential to have good distant muscle balance as so-called "fixation" or reading distance balance.

The chief difficulty in eliciting ocular muscle errors is that it requires time. Secondly, these errors which are manifest are usually not troublesome except in the production of localized eye-muscle pain. The hypertensive muscle is not infrequently painful and, although the error is a manifest one, the muscle may require symptomatic operation for the relief of spasm.

The time element is important to differentiate between instability secondary to general physical debility or primary instability of the ocular muscles themselves. Patients must be

THE OCULAR MUSCLES. A MEDICAL PROBLEM!

A. D. RUEDEMANN

THE problem presented by the patient who has been referred to the eye department because of head pain, headache, and other more or less vague general symptoms, is often very difficult. Such a patient is usually having genuine discomfort, although often his trouble is classified as neurasthenia, nervous debility, hysteria, constitutional inferiority and a host of other vague terms. Careful study reveals the fact that patients of this type may have suffered since early childhood with their ailments which have become increasingly more severe and that some of them have undergone numerous and varied forms of treatment without relief. The strain on the visual apparatus in our modern life is terrific and the oculist must be careful and thorough in his investigation before he classifies his patient as having perfect vision.

The study of the ocular muscles leads one into general medicine, orthopedics, neurology, and, remotely, psychiatry. The overlapping of ophthalmology with other branches of medicine is well known. That it overlaps so frequently and to such marked extent in the field of muscle imbalance may be generally known but certainly is not generally applied. In order to see any object, the primary action is to move the head into a position so that the eyes are directed toward the object to be visualized. This primary movement is made by the muscles of the neck, often acting alone, although it is not unusual for a person to turn head and shoulders, or head, shoulders and thorax or he may even turn completely around before the external eye muscles are brought into play. The neck muscles place the eye in position for the external eye muscles. With the latter, they fix the maculae and the ciliary muscles accommodates and attempts to focus. These three associated systems

refractive error whether it is farsightedness or nearsightedness, with or without astigmatism, without some resulting fatigue.

Errors of refraction, whether congenital or acquired, are a distinct clinical entity, require careful study and, in association with muscle errors, may elude the most careful oculist unless the entire picture is before him. Except in a very few cases no examination may be considered complete notwithstanding the contrary opinion of many reputed oculists without sufficient cycloplegia. From my experience it would seem that too few men can do a good manifest refraction to rely upon this alone as a routine procedure.

Medical indifference is undoubtedly responsible for the patient's dilemma. Any refraction is not a refraction at all. The responsibility of careful study of the many factors entering into the causation of a refractive error, its variabilities, and the many contributing factor, requires skill, training, and experience. Unquestionably, too often the proper adjustment of glasses is looked upon by most general medical men as a matter of little consequence.

The amount of error, the necessity for glasses, the type of glasses to be worn, whether they should contain any protecting tint or not, and other technical problems are of utmost importance in giving the patient comfort and providing him with the last physical necessity to allow for the complete mental picture which is provided for by fusion. Fusion is the completed visual impulse and if there is any functional or mechanical error, the visualization of objects is sure to be accompanied by effort and rapid fatigue. Unequal refractive errors, anisametropia, provide unequal images and are confusional; muscle errors allow pictures to overlap as well as marginal blurring, are fatiguing and may make fusion almost impossible. With a manifest squint, there is no fusion, for the patient is using but one eye and is comfortable unless he has a spasmodic muscle which is painful.

Binocular vision may be entirely absent even with two relatively straight eyes. A special examination is required to

studied early in the day before work, late in the day, late in the week and frequently must undergo examination after a period which, of their own admission, may give a clue to a specific period of discomfort.

There are two main groups of ocular muscle imbalance—the divergence excess or weakness of accommodation convergence group and the convergent excess or divergence weakness group and more rarely, but with many symptoms, there is a small group in which vertical errors are predominant.

Careful history often brings out an hereditary factor in these cases, as shown by repeated fitting of glasses, slow reading, lack of concentration, and innumerable other symptoms. Previous operation on the muscle does not always mean relief of symptoms for there are many patients who apparently have no mechanical difficulty but still the function of accommodation is impaired. This group frequently has latent errors—errors never apparent but always present and not always severe, but constantly contributing their share to the nervous instability of the patient.

The picture, to be clearly perceived, must further be brought into proper focus by the action of the ciliary muscle which is again constantly in use and is the source of a tremendous amount of pain, both localized and referred. The ciliary muscle, although involuntary in action, is associated actively with the many voluntary visual impulses. Some activity is required of the ciliary muscle every time an object is glanced upon. Many patients are unaware of the fact that ordinary occupations frequently require tremendous ciliary effort. The advances of civilization require less actual physical effort but the ocular effort is magnified by the increasing speeds of machines, their intricacies, the lengthening of the day's activities and the increase in reading and school work. Although other physical activities have been decreased, the demand on the ciliary muscle keeps on from birth to death, from daylight to bed, and then frequently there is a last reading effort to exhaust the ciliary muscle completely and put the patient to sleep. No amount of ciliary effort can overcome any degree of

eral weeks of rest and then examinations. Short daylight hours, insomnia and long use of the eyes are often too much and for many, school becomes a demon of impossibility. From January examinations to the Easter holidays, many are forced out of school by failure of the eye muscles. As the spring holiday approaches and the days get longer, many are prevented from failing, but the last weeks may incapacitate them. As one student aptly said, "I was dragging along until final examinations and then I was licked for ten days after returning home. I was unable to use my eyes at all."

Many ordinary occupations require high-speed muscle balance and constant attention. It is necessary to elicit the hours of work, of play, and of sleep, for many patients through lack of intuition are unable to link up signs and symptoms with use of their eyes, but questioning them helps them form associations and soon they reveal the chain of events in their case. Carsickness, shopping headaches, failure to enjoy crowds, being bored by guests, inability to look some one in the eye may all be symptoms of ocular muscle deficiency.

Certain signs of ocular muscle dysfunction manifest themselves early and carry on throughout life unless corrected. Perhaps the most outstanding is a head tilt, practically always due to a vertical muscle error. This may be evident early in life and every photograph will show the head carried in the same lateral position. Some of these cases are severe enough to be classed as torticollis and, in most instances, the neck muscles can overcome considerable vertical error but it is done at the expense of the patient's comfort and overdevelopment of one or more of the neck muscles. Secondarily, there is usually an associated facial deformity which is a compensatory hypertrophy.

More frequent and difficult to estimate are the hypertrophies of the neck muscles due to the horizontal group of eye muscles. There is a constant holding of the head in a fixed position to get the eyes in primary fixation but also to aid the eye muscles because of their deficiency. In such patients, the posterior muscles are manifestly increased in size out of proportion to the

ascertain this and should be a part of the routine procedure in making a complete study. It is necessary to determine whether fusion can be maintained without effort in all cases of fatigue.

A car approaches over the crest of a hill and immediately there is a response—is it one or two? The speed of the object is estimated and the neck is turned to give the eyes a central stance and the external muscles adjust themselves to allow the maculae straight ahead fixation whenever possible and the picture is mentally noted. Repeat this over and over and one becomes conscious of the tremendous amount of nerve energy and reflex response necessary to use the eyes over extended periods of time. Magnify this several times in reading and several times more in the activities of modern life and one can realize the extent of physiologic response which is necessary.

The patient's history is extremely important in cases of ocular muscle imbalance. Perhaps no other branch of ophthalmology requires more persistent questioning because of the reluctance on the part of many patients to associate the eyes with their physical debility.

It is characteristic in such cases that there is a certain chronicity of symptoms. These may be constant but they may also appear for a period and recur. The time of first appearance of discomfort, early history in school, whether the patient is a fast or slow reader, and his scholastic standing are important considerations. Whether school is a pleasure or a bore, the amount of time spent in study, the oft-repeated statement that a youngster formerly had a high "intelligence quotient" and is now slow in school, restlessness, inattention, and lack of concentration are all clues to ocular instability. Nervousness, irritability, and the nervous breakdown in the spring of the year is a definite part of the clinical picture in this group of cases.

In grouping a large number of students as to time of onset of symptoms, one is impressed by the periodicity of their complaints. They complain but little in the fall after a summer of rest. As the holiday season approaches, they suffer more fatigue and usually they struggle through to vacation period, with sev-

ficient to cause loss of appetite and loss of weight, is a common symptom. This discomfort is a costly one as many such patients are led through innumerable x-ray examinations and medical studies and often have enough discomfort to insist on an abdominal exploratory operation.

The severe nervousness in youngsters often leads to psychiatric investigation. Inattention leads to poor scholarship and the child may become a difficult problem. Not unusual is a history of "spells" similar to attacks of epilepsy and the lessening of the number of such seizures and the improvement in the patient's general disposition are definite and progressive with improvement in the muscular balance.

Hypothyroidism, hyperthyroidism, progressive myopia, and postencephalitis usually are associated with a weakness of accommodation convergence.

The so-called Möbius sign usually corrects itself with the relief of hyperthyroidism; it is not constantly present, may persist after surgical or medical relief and when it does, it presents itself in the inability of the patient to return to ordinary use of the eyes.

There are two types of hypothyroidism in which the function of the eye muscles may be impaired. The first is the post-surgical hypothyroidism, with or without exophthalmos. Patients with this condition frequently have a weakness of accommodation convergence which adds to their general fatigue and, unless this is corrected, these patients have a great deal of difficulty in carrying on with their work. The second type of hypothyroid patient has edema of both upper and lower lids and but few other signs of hypothyroidism except a persistently low basal metabolic rate. The muscle error in such cases requires general treatment with the eye exercises before relief can be secured.

Progressive myopia simulates the second type of hypothyroidism and is usually associated with a low basal metabolic rate, and the patients seem to be benefited by thyroid extract, although it is likely that the underlying cause is a polyglandular disturbance.

general build. Large sternocleidomastoids, large trapezii, and other posterior neck muscles are not uncommon. No physical examination of patients suffering from questionable general discomfort should be considered complete without a close observation of the contour of the neck and carriage of the head.

The facial expression of the patient is very important—vertical frown, “crows’ feet,” inequality of arching of eyebrows, and all unusual facial distortions often may be traced to ocular origin. Orbicularis spasm may be muscular but is most frequently refractive. Blepharitis marginalis sicca and marginal hyperemia may be of muscular origin.

General signs and symptoms reflect the chronicity of the imbalance, not always its degree. Muscle pain may be due to a single spasmodic muscle and the pain is local and unilateral, probably the only unilateral eye pain of muscular origin. Most all eye discomfort is bilateral whether in the eyes or in the head. Frontal pain referred bitemporally is an ache which may become very severe and simulates the pain of a brain tumor or migraine. The third and most common pain associated with the muscle error is neck pain along the muscle attachments which is severe and deep and often mistaken for and treated as a cervical arthritis without result. It is persistent pain, not relieved by sleep; it comes on in the early morning and becomes severe enough to necessitate sedatives, and is sometimes confused by examiners with a cerebellar lesion. The neck pain may radiate along the muscles to their origin, to the shoulder, down the back and, because of faulty shoulder position, down the arm. The stiff neck of the automobile driver and the fixed position of a machinist’s head indicate muscle imbalance and lead to early afternoon fatigue.

Accompanying head pain are nervousness and irritability, the latter may go on to a definite change in personality. The inability to take care of children because of lack of patience, short temper, lack of concentration, unhappiness, boredom of housework, such as ironing, mending, dusting, etc., are frequently traceable to eye-muscle defects. Epigastric distress, a feeling of nausea which rarely goes on to vomiting but is suf-

problem can hope to arrive at conclusions by a single observation. Thorough complete cycloplegia is necessary and atropine or scopolamine may have to be used, especially in hyperopia with esophoria.

The place of work, the type of work, the hours and, in certain instances, copies of the work should be investigated. For example, if a patient with exophoria is attempting to chart stock quotations in 5 mm. squares by quarter divisions, no amount of muscle correction could ever make this man comfortable.

Treatment for the various muscle errors can be and is successfully carried out by ophthalmologists. The main requisite to therapeutic success is patience, not because the treatment is difficult, but because the patients are of the type not prone to follow advice or treatment. The second requirement is time. It requires office time and the duration may extend beyond what most patients feel should be devoted to their own recovery. The medical man may be of great assistance in this regard by insisting on the patient's cooperation, for without it success is impossible.

Prism exercises, ordinary finger-to-nose exercises may be all that is necessary. However, the patient may have a beginning amblyopia and require covering of an eye for a period and then treatment with Worth's amblyoscope followed by other training exercises, as outlined by Wells, Worth, Peters and others. Errors that are too high in degree may require operation to put the muscles in position for possible treatment. Surgery in itself is not a cure—a large number of our patients have had operations with a good cosmetic result; their eyes are straight but they have persistent low-grade uncorrected muscle errors. Treatment is incomplete without establishing proper fusion and may better not have been attempted in many instances. The patient who is allowed to develop an amblyopic eye is probably better off than one who has troublesome muscle imbalance.

The following cases illustrate some of the problems presented by imbalance of the eye muscles.

There is a large number of patients who have weakness of accommodation convergence and rapid muscular fatigue after encephalitis. They appear to be quite like the hypometabolic group although stramonium rather than thyroid extract is of the most value in the treatment. As a rule such patients are unable to use the eyes to any extent and complain bitterly when it becomes necessary to use the eyes at all.

Single muscle paralysis and weakness are found in a larger number of diseases and, although they do not always produce a diplopia, they require careful study. Syphilis, diabetes, focal infections, and hyperthyroidism may affect one or more muscles, causing the patient to be unable to use his eyes because of the resulting disability. Posttraumatic orbital changes, whether following pulsating exophthalmos or globe displacement may leave the muscle relationship in a poor condition and, after a period of time, this should be studied for evidence of error. Any condition producing exophthalmos, whether unilateral or bilateral, disturbs the muscle balance, and, if the general condition is corrected, the local dysfunction may not be completely relieved and may necessitate special study and treatment. Any severe debilitating disease may bring out a previous muscle weakness. Effort of reading may be brought out during the illness or later when the patient attempts to return to work.

Muscle instability, muscle error, and fatigue are commonly associated and, in order to determine the part the eyes play, we have devised a careful study which is used routinely in all cases referred to the eye division. Sometimes merely having the patient fix on an object and then cover and uncover the eye may reveal an error. The use of a fixation light and placing a red light over one eye may bring out a latent diplopia. However, all phases of muscle balance must be studied by the Maddox rod, rotary prisms, and various duction tests. It has been necessary in some instances to use the "Marlow" cover test which has proved itself very useful in other cases. If repeated studies are made, early in the morning, early in the week, late in the day or week, the lack of proper muscle activity may be demonstrated. No one attempting thorough investigation of the

Case V.—A school boy, aged ten, complained of pain on using the eyes and carried his head to one side. Examination in 1925 showed the following: Vision, O.D. 6/7.5; O.S. $\frac{1}{10}$; accepts plus 2.50 with plus 0.75 axis 90° $\frac{1}{2}$ O.D. plus 2.25 with plus 0.75 axis 90° $\frac{1}{2}$ O.S.; muscle 10° left hyperphoria; (under cover) 18° left hyperphoria; 3° esophoria; and left eye spasm of left inferior oblique muscle. Tenotomy of left inferior oblique muscle was performed but the patient still complained of some difficulty with reading and close work. Eight years later, in 1933, examination showed 4° right hyperphoria. He was then given 105° base down O.D., 1 base up O.S. The patient's head is now straight and he is quite comfortable.

In a family of five girls, three had convergence excess. They all disliked reading and school work, were bored, and found it a definite effort to get their lessons completed. All complained of being tired at the end of the day. Stereoscopic exercises were prescribed for them and they were restored to comfort in school.

In spite of the diversity of the errors and their complexity, every patient is entitled to treatment because of the satisfactory end-results obtained with proper glasses and exercises. Complete relief of symptoms and economic rehabilitation are frequent and there are no more grateful patients in medicine than those who have been relieved of an ocular muscle imbalance.

Case I.—An accountant, aged thirty-five, sought treatment because he was nervous and irritable and suffered from gastric distress. He was unable to carry on with his work because of ocular fatigue. Ophthalmoscopic examination revealed vision $\frac{1}{2}$ %. There was a refractive error, slight astigmatism and the muscles showed excess convergence. Operation was performed on the left external rectus muscle and the patient was able to resume his activities aside from heavy use of eyes during the day.

Case II.—A woman, aged thirty-five, had been treated medically for enteroptosis and undernutrition. The eye examination showed a refractive error, O.D.—0.50 plus 1.00 axis 90; and O.S.—0.50 axis 180. Treatments with muscle exercises and prism base were of no avail, and further muscle correction was accomplished by operation, after which the patient's entire general discomfort was cured. The patient brought in her daughter, aged twelve, who had similar complaints and was found to have a similar eye condition, muscle imbalance.

Case III.—A man, aged forty, employed as a chemist, suffered from headaches which had been diagnosed as of the migraine type. The patient had known of ocular muscle error for nine years and complained that he could not concentrate and was nervous. Tenotomy of external rectus was performed and after the operation the patient experienced complete recovery and had no headaches. His daughter, aged ten, has a similar muscle error and is improving definitely with exercises.

Case IV.—A woman, thirty-four years old, had nervous indigestion, visceroptosis and a low basal metabolic rate, minus 16 per cent. She had had ocular hemorrhages about eight years before and had had recurring headaches which had raised the question of migraine. She was unable to read for any length of time. Ophthalmological examination revealed marked convergence excess and a bad error of refraction. The proper glasses were prescribed and muscle exercises were carried out with the result that the patient's headaches were completely relieved and she was able to read and use her eyes.

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THE TREATMENT OF DIGESTIVE DISTURBANCES IN ASTHENIC PATIENTS

C. L. HARTSOCK

THE group of patients with functional disturbances of the gastro-intestinal tract resulting from asthenia is one of the largest and most difficult with which the physician and gastro-enterologist has to cope. The digestive symptoms of the visceroptotic, the emotional, the constitutionally inferior, and the mentally harrassed patient can be attributed chiefly to easy fatigability and resultant nervousness. Because of their nervous and emotional instability they frequently are mismanaged by the physician and constitute a large part of the practice of the quack, cultist and diet faddist. It is true that the methods of these healers appear worthless from a scientific viewpoint, but the highly emotional character and the illogical reasoning of many of these patients make it necessary that cures be effected more through an appeal to their emotions than through scientific management and reason.

If the medical profession is going to assume a critical attitude toward those who practice mental healing, they must accept the responsibility for the large number of patients who require a touch of voodoo and must try through a combination of art and science to give these patients more comfort than they can get elsewhere. Perhaps in a large clinic where there is so much emphasis on scientific facilities, these patients cannot be treated so satisfactorily though it seems that this should not be so. This same scientific equipment which has tended to make the modern doctor lose the art of medicine paradoxically possesses the highest possibilities of suggestive and psychic therapy if used properly. Too often, however, through lack of interest, both the art and science of medicine are neglected in the management of the asthenic, chronic dyspeptic and mentally harassed patient.

The treatment and prognosis in this group of patients is made much easier by having some workable classification. There is no satisfactory anatomic or pathologic classification, but the patients do fall into several definite clinical groups, which can be recognized rather easily.

CLASSIFICATION

Group I.—The first grouping is of those who are constitutionally inferior. Such patients frequently are referred to as having the Stiller or Adler syndrome. They have a poor nervous and physical constitution, which is entirely inadequate to cope with the ordinary problems of life. Naturally, with poor basic material, the prognosis is poor for rehabilitating the patient to the extent of making him a useful person, but often he can be benefited if the physician helps to solve many easy everyday problems which are a burden to him.

Group II.—In the second group are placed the mentally active and ambitious, who have a poor physical constitution by heredity or early environmental influences, such as some nutritional problem, rickets or childhood tuberculosis, or other chronic illness during the developmental period. They usually have anatomic visceroptosis, known as Glénard's syndrome. They get along fairly well in life, but do not realize the limitations of their physical strength and their ambitions lead them into a breakdown with resulting gastric symptoms from the visceroptosis. The outlook for improvement is good, but recurrences are frequent unless the patient can be made to realize the importance of leading an orderly and systematic life.

Group III.—The patients in the third group have normal constitutions but through sickness, repeated pregnancies, overwork, etc., have been completely worn out and have lost considerable weight. Too strict dieting either for reducing or because of some slight digestive disorder often results in excessive loss of weight and weakness. A short period of rest and other hygienic measures will assure complete recovery of the patients in this group.

Group IV.—This group includes those also of sound constitution, who are inclined to be erratic and emotionally unstable. This includes a large group of young girls and women in whom frustrated desires, undue anxieties and too much emotional excitation interfere with proper digestive function. This group differs from the one above chiefly because of the emotional element. The prognosis, for this reason, is not quite so good, because emotional excitement may bring about a recurrence of symptoms.

SYMPTOMS

It is easily seen that this is purely a clinical classification and does not depend so much on the symptoms and physical examination of the patient as upon a careful psychic evaluation of the patient during the taking of the history and a careful analysis of the environmental and nervous factors at the onset of the condition. After the original onset, the symptoms are so distorted and exaggerated by fears, anxieties and the various therapeutic efforts that the final picture does not depict the true situation.

As these patients present themselves to the physician, their complaints are referred chiefly to the digestive and nervous systems. However, their complaints are usually legion. The most frequent and characteristic symptom referred to the stomach is pain coming on immediately after or during a meal. This is located in the epigastrium, usually not lower than the umbilicus and when carefully analyzed is not a pain but a heavy feeling of fulness or discomfort. There is usually a lack of appetite, especially if the patient is tired. Frequently, however, the patients think they have a ravenous appetite but this is completely satisfied with a few bites. They generally feel better if they do not eat and this is one of the most vicious symptoms they could possibly have as it leads to further loss of weight and weakness and causes the condition to become progressively worse. Real pain is infrequent. Other commonly associated complaints are belching, gurgling sensations and noises and distress in the lower right quadrant, chronic obstinate constipation, bad breath and coated tongue.

They are emotional, anxious, have numerous fears, dizzy feelings, fainting sensations or real syncopal attacks. Nocturnal panicky attacks associated with tachycardia, palpitation and a fear of death are not common. The patients either are chronically tired or have bursts of energy followed quickly by fatigue. They may have insomnia or excessive drowsiness. Headaches usually are frequent. Naturally of the introvert type, they imagine all sorts of conditions as the cause of trivial symptoms.

PHYSICAL FINDINGS

Physical examination of the severe cases shows a tired, nervous person of the microsplanchnic hypovegetative type and usually 20 to 50 pounds under ideal weight. The features are sharp and pinched, the chest is long and narrow in the anterior-posterior diameter, with stooping of the shoulders and sunken infraclavicular spaces. Expansion is limited and diaphragmatic breathing is shallow or absent. The chest frequently shows signs of childhood rickets. Auscultation and percussion of the lungs give little information, although old chronic fibroid or glandular tuberculosis frequently is present. The heart is of the hanging type and almost invariably a faint systolic murmur is present at the pulmonic area. The blood pressure usually is low. There is a tendency to tachycardia and an unstable vasomotor system, which is the cause of some very annoying symptoms.

The abdomen is of the scaphoid type, with lax thin walls. The recti are poorly developed and marked bulging of the lower quadrants are frequently seen, due to weakness of the oblique muscles. In the erect position the lower abdomen sags out and the upper is concave. The application of Glénard's test, that is, to stand behind the patient and with both hands flat on the abdomen to determine the relief which the patient receives with an elevating and pressing motion, is useful to determine which patients will get relief from supports. There is usually a general abdominal tenderness, which is most constant in the epigastrium and in the right lower quadrant, where distention of the cecum secondary to a spastic colon frequently may be felt.

This is the reason that appendectomy so often is performed with poor results. By grasping both flanks just under the costal margin between the thumb and forefinger and having the patient breathe, loud borborygmus can be heard, caused by displacing the fluid levels in the ptosed stomach through its compressed lumen. Occasionally, patients learn to produce a succussion splash, and it becomes a great annoyance and obsession to them. The forward protrusion of the lower abdominal segment is usually associated with an increased lumbar lordosis. In nearly all instances, the right kidney can be palpated. In women, functional dysmenorrhea is common.

Special examinations should include a careful search for foci of infection. Obstruction to nasal breathing should be especially looked for. On account of the marked asthenia, eye muscle errors are frequently present.

A roentgenogram of the chest never should be omitted in the examination of this type of patient, but it is an exceedingly delicate matter to know how much to discuss with the patient, if some questionable findings are present. Except in cases of definitely active tuberculosis, it is much better to leave the patient entirely unaware of any specific findings, and if treatment is necessary, it should be given under the guise of other therapy.

LABORATORY FINDINGS

Complete gastro-intestinal and chemical studies should be routine procedure. They are of distinct psychic benefit and frequently disclose unsuspected lesions. The test meal should always be done as it gives important therapeutic information. Achlorhydria is not infrequent, and hypoacidity is the rule but sometimes very high acidities occur and this information is very important from a therapeutic standpoint. Examination of the stools is omitted entirely too often. It is true that usually it gives very little helpful information but the psychic benefit of the examination is great.

Routine blood studies usually show an anemia of the hypochthemic, normocytic, normochromic type. This is the type which gives a very poor response either to iron or liver therapy.

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The basal metabolic rate is usually low in spite of symptoms which mildly suggest hyperfunction of the thyroid gland. In many cases the low metabolism is the result and not the cause of the asthenia. The only accurate means of determining the need of thyroid substitution in these cases is the therapeutic test.

DIAGNOSIS

The only difficulty with diagnosis is that it is too simple and one may for that reason be inclined to omit some of the necessary investigative work. An unsuspected lesion may be overlooked in this manner or the physician may thus fail to take advantage of the powerful psychic weapon of a thorough examination that helps to inspire the confidence of the patient. Although he may not realize it, the physician himself acts in a much more confident manner when he has all the facts at his finger tips and can not be tripped by an unexpected question of the patient about some fear of disease in some location which the patient thinks should have been more thoroughly investigated.

With a complete diagnosis established, and the patient classified in order to have a better idea as to prognosis, the next and most important step is the treatment.

TREATMENT

Treatment should be considered under the heads of (1) psychotherapy, (2) rest, (3) treatment of general conditions, such as foci, etc., (4) diet and gain of weight, (5) care of bowels, (6) medication; general, glandular, vitamin preparations, (7) physiotherapy; exercise, baking, massage, colon irrigations, supports, (8) surgery, and (9) regulation of life and prophylaxis.

Psychotherapy.—To consider this in more detail, psychotherapy is a vague term. It is mentioned glibly in many articles, but seldom is there any mention of the details of the psychotherapy employed. The reason for this is that every case is different, but there are a few fundamental principles which should be thoroughly understood.

This is the reason that appendectomy so often is performed with poor results. By grasping both flanks just under the costal margin between the thumb and forefinger and having the patient breathe, loud borborygmus can be heard, caused by displacing the fluid levels in the ptosed stomach through its compressed lumen. Occasionally, patients learn to produce a succussion splash, and it becomes a great annoyance and obsession to them. The forward protrusion of the lower abdominal segment is usually associated with an increased lumbar lordosis. In nearly all instances, the right kidney can be palpated. In women, functional dysmenorrhea is common.

Special examinations should include a careful search for foci of infection. Obstruction to nasal breathing should be especially looked for. On account of the marked asthenia, eye muscle errors are frequently present.

A roentgenogram of the chest never should be omitted in the examination of this type of patient, but it is an exceedingly delicate matter to know how much to discuss with the patient, if some questionable findings are present. Except in cases of definitely active tuberculosis, it is much better to leave the patient entirely unaware of any specific findings, and if treatment is necessary, it should be given under the guise of other therapy.

LABORATORY FINDINGS

Complete gastro-intestinal and chemical studies should be routine procedure. They are of distinct psychic benefit and frequently disclose unsuspected lesions. The test meal should always be done as it gives important therapeutic information. Achlorhydria is not infrequent, and hypoacidity is the rule, sometimes very high acidities occur and this information would be important from a therapeutic standpoint. Examination of the stools is omitted entirely too often. It is true that examination of the stools gives very little helpful information but the psychic benefit backs the examination is great.

Routine blood studies usually show an anemia of the hypochromic, normocytic, normochromic type. This type of anemia gives a very poor response to iron or

amount of daily rest, and directly proportional to work and strain. These patients were never constituted to carry on what is commonly considered a day's labor, and early in life they have exhausted their reserve vitality and have gradually depleted it further to the point of complete exhaustion. Prophylaxis or preventive medicine is of the utmost importance. Many of these patients are high school and college girls and boys. Some advice to the parents and the patient about rest, the type of future livelihood, the importance of restraining the overly ambitious, may keep this girl or boy going above the level of a useless individual. Some mention of birth control in suitable cases is important. One or two children may be the salvation, more, the downfall of the patient.

In a specific instance the amount of rest is, of course, proportional to the severity of the condition. Many patients require complete rest in bed for long periods of time. Nearly all should rest after meals. Others only require more frequent and less strenuous vacations. This latter applies especially to school teachers, who frequently take up post-graduate work and summer teaching, when really nearly all of them require a complete rest from the strenuous school session. Whatever the amount of rest needed, it should be regular—without exhausting influences, such as friends coming in as Job's comforters and children annoying their mother. It must be remembered that monotony is one of the most exhausting of all things, and suitable efforts should be made to relieve this.

General Conditions.—Little is to be said about the treatment of general systemic conditions. As a rule this phase of treatment is overemphasized or begun too soon, before the patient's vitality will stand such procedures as extraction of teeth or tonsillectomy.

Diet.—No specific diet can be mentioned to cover all cases. In general, the patient should have a high-calorie, high-vitamin diet of the smooth, easily digestible variety. The symptom of heaviness after a meal is due to an atonic, fatigued stomach, which is not capable of strong peristaltic movements to carry the food along. The symptoms increase in proportion to the size

Briefly, psychotherapy is leading the patient from a depressed, discouraged, anxious mental state to a more optimistic and encouraged outlook. Fear is changed into confidence through suggestion alone. The physician can practice very few of the voodoo or mesmeristic arts without soon being looked at somewhat askance, but he can practice honest suggestive therapy. In the first place, careful attention to the patient, giving him plenty of time to tell his story, and, a complete examination form the entering wedge to a patient's confidence. From then on it is a little more difficult. The physician must assume an air of complete confidence, even though he does not feel it. Complete and detailed instructions must be given, and no annoyance can be shown when the patient needs repeated instructions about some trivial detail of treatment. Care must be taken in the manner in which these findings are described to the patient. Simple, understandable explanations of symptoms, using simple analogies, often clear up causes of anxiety. No talk to the patient should be complete without saying there is no sign of cancer, or anything that will cause cancer. The prevalence of cancerphobia among patients of this type is amazing. It is better not to mention a low stomach. Most symptoms and conditions are best explained on the basis of fatigue and exhaustion, rather than nervousness. Lastly, the physician must not be discouraged because results are slow, especially if the patient falls in Group I where any noticeable benefit is very seldom obtained. The doctor must seem enthusiastic, as long as the patient will stay with him. Many of these patients come to the physician for sympathy and confession, and even though they apparently multiply their complaints every time they come, they probably do derive some benefit in coming, or they would stop. If a doctor is unwilling to practice this kind of medicine, this type of patient should be referred as soon as possible to someone who will, or they soon will be getting their backs twisted, wearing charms or embracing some other type of unorthodox treatment.

Rest.—The question of rest is an exceedingly important one. The patient's symptoms are almost in inverse ratio to the

many advertised laxatives or to the irrigation enthusiast and the cathartic and irrigation habits are difficult to eradicate. With diligent care, however, most patients can secure natural elimination. It requires consideration reeducation of the patient by the doctor and an enormous amount of cooperation, understanding and confidence on the part of the patient but the results are well worth the time of both.

To some extent, it is important to know something about the condition of the colon in order to form some opinion about treatment but the treatment differs very little except in intensity and duration. For example, the simple constipation of faulty habits and the mildly spastic colon yields quickly to treatment and gives brilliant results with simple measures while the huge dilated redundant colon, the markedly atonic right colon, the colon with sharply augmented hepatic and splenic flexures, and the ptosed transverse colon require long, protracted and elaborate treatments. To begin treatment without some previous knowledge as to the results to be expected means failure as the patient will surely be discouraged without forewarning in this respect.

The following routine will yield results in practically every case, allowing for variation in the intensity of the procedures.

First and most important it is necessary to convince the patient that laxatives must not be used regularly in any form and that for a few days after the treatment is started a bowel movement is not necessary. Enemas and irrigations as usually taken must also be discouraged.

The second important educational step is the cultivation of a habit time. Corresponding with the physiologic movements of the colon, the ideal time for this is after meals and as one movement a day is usually sufficient, the best time is after breakfast. The breakfast should include at least a pint of some type of hot drink, and should be followed by an interval of waiting at least fifteen minutes during which a walk or some exercise may be helpful. At this time an attempt to secure evacuation should be made and at least twenty minutes should be given to the effort. If unsuccessful during the first two days of treatment, a

of the meal, and for this reason meals should be small and frequent, with the total day's calories well above normal requirements. The patient must be warned that some distress must be borne at first in order to get adequate caloric intake to secure complete relief later, as the muscles become stronger. Care must be taken to serve appetizing foods in a way that is pleasing to the eye and sense of smell. This is a small thing, but exceedingly important to the jaded appetite. It is much better for a mother to try to get the children's meals out of the way, and then eat her own in peace. The slightest annoyance often takes away the little appetite the patient may have.

Alcoholic liquors should be considered under the diet and the small stimulating cocktail may be helpful. Light wines are especially good. To those who relish it, beer is an excellent source of food and calories and apparently contains great weight-increasing properties. Tobacco should be entirely eliminated. It seems to exert a detrimental effect on the appetite, even though "it satisfies."

Moody, Von Nuys and Chamberlin have shown conclusively that visceroptosis *per se* is not a cause of symptoms. Unquestionably, however, it is a predisposing factor in causing disturbances of motility and efforts must be made to try to improve motility. Increase of weight improves motility more through separating and ironing out the acute angles of the intestinal coils, than through any marked elevation of the viscera.

Gain of weight is, of course, accomplished largely through rest and a high caloric diet, but of recent years insulin has been used to help accomplish this, with very good results in many cases. An increase of metabolism or oxygen consumption through proper exercises, especially breathing exercises, in conjunction with insulin gives surprising results in some instances. Both of these will be discussed more fully under separate headings.

Care of the Bowels.—The correction of constipation is by far the most difficult feature of the treatment in the majority of these cases. The cathartic habit has been firmly established. The patients are bowel and stool conscious and fall easy prey to

invaluable help, both to relieve distress and to help elimination. Relaxation may be secured further by some mild sedative and atropine or belladonna. This can also be discontinued with improvement but I suggest that patients use it at periodic intervals, especially when they are under a nervous tension or during excitement.

In patients with the atonic type of bowel, supports, physiotherapy and exercises are of great help. Vitamin B in large quantities seems also to aid materially. The metabolic rate frequently is low and when indicated, to obtain any results at all, thyroid must be supplied in sufficient amount.

I have no criticism of the occasional laxative. It even seems helpful in patients with migraine headaches and bilious attacks but caution must be used that the routine is not upset by the complete evacuation of the intestinal tract. The routine used in the beginning of the treatment should again be instituted after the cathartic as several days will be necessary to allow the normal progression of the intestinal contents to the rectum.

The barrier of constipation passed, a great deal has been accomplished toward the success of treatment.

Medication.—As can easily be seen, there is nothing in the way of medicine that closely approaches specific therapy. The usual question to decide is whether the patient needs a sedative or a stimulant. As a rule, the stimulants are indicated to give increased tone to the stomach and bowels. Tincture of nux, gentian and quinine and hypophosphites are the most frequently used. Every physician has his own preferred prescription and one is probably as good as another. Sedatives would seem to be contraindicated if stimulants are needed, but most of these patients are so fatigued that they can not relax and secure their needed rest, and I have found that they usually improve more when both are used, a stimulant before meals to increase the tone and appetite, and a sedative after meals to get better relaxation. Small doses of the triple bromides, hyoscine and luminal are the best in the latter series. At times there is a lack of tone of the stomach and bowels, with an increased tone of the

glycerin suppository or a small enema not to exceed one pint of plain warm water given daily until natural results are obtained. One realizes that the morning rush of the average American does not lend itself well to this routine but usually the patient can be convinced to try it for a short time, after which the good results will cause a further continuance.

The importance of the smooth low-residue diet has been mentioned previously. The teaching that a coarse rough bulky diet is the proper correction for all constipation has been so firmly rooted in their minds that these patients go to extreme lengths in this direction. The simplest way to teach them the folly of this is to explain that the cause of their constipation is fatigue and weakness of the gastro-intestinal tract, which corresponds to their general fatigue. The bulky diet causes further debility and irritation and also cuts down materially the caloric intake which is necessary to build up their strength. The bulk of the diet can, of course, be increased with improvement in the general condition.

If more bulk is necessary it should be supplied in a smooth and nonirritating form such as agar and psylla seeds, for they have the further advantage of preventing excessive dehydration of the stool. I routinely prescribe these at the beginning of treatment and gradually reduce the amount as soon as advisable. If the patient can tolerate the extra bulk, I give quite large doses at first as there is nothing that pleases the patient so much as the first natural bowel movement. Occasionally, even this type of bulk will cause distress and must be discontinued. To counteract the tendency of the psylla seeds to become packed in the cecal region and cause distress, I always give mineral oil, preferably in the emulsified form. It is surprising how rapidly these substances can be reduced in amount or completely eliminated. It is of course important to assure the patient that the action of these is entirely different from that of a laxative. It is also important to give warning that laxatives are concealed in so many proprietary preparations of similar nature.

For the patient who has a spastic bowel, a short rest after meals with heat to the abdomen such as an electric pad is of

brilliant response to vitamin feeding alone, but they all should be given routinely, especially vitamin B, which stimulates the appetite and helps to increase weight.

It might be expected that glandular products would offer some help in the treatment of patients with functional gastric disturbance. In the past few years insulin has been used a great deal in the treatment of the tuberculous and the asthenic, malnourished person. A high carbohydrate diet is given and from 5 to 20 units of insulin are given twenty to thirty minutes before meals. The dose is low at first and is gradually increased to the point of tolerance, as indicated by mild reactions and then decreased again to a point just under the tolerance dose. In most cases, there is a decided increase in appetite and consumption of food, which frequently leads to a gain in weight.

In spite of the fact that most asthenic patients are thin and nervous, their basal metabolic rate usually is low, and it is difficult to judge whether this is a cause or result of their condition. In all cases in which the metabolism is decreased, and in some showing normal metabolic rates, I give small doses of thyroid after a patient has had a short period of preliminary rest treatment. Some can tolerate quite large doses and feel definitely better, while others are made worse and thyroid has to be eliminated. A brief course of thyroid as a therapeutic test can do no harm, and it is well to remember that hypofunctioning thyroid does not always cause obesity, sluggishness, etc. It seems paradoxical but a sedative used with thyroid often gives brilliant results.

One would think that cortin would be an excellent preparation for asthenia of all types. At the present time it is too expensive and also not available in sufficient amounts for trial in such cases, but reports of trial in cases somewhat similar definitely show that it is not a panacea for easy fatigability. If there are definite clinical indications for the hormones relating to sexual and reproductive organs, they should be used.

Unquestionably, some patients are benefited by large doses of calcium. I believe this is due to a deficient calcium diet, rather than real hypoparathyroidism. At least parathormone

sphincters. In these cases belladonna or atropine is advisable. In severe cases with marked gastric intolerance to all drugs, sedatives are best given as suppositories.

As mentioned previously the anemia usually is of the type that does not respond to iron. A few of these patients have the achlorhydric, microcytic type of anemia and make a marvellous response to iron. Usually I try iron in all cases in order to be certain whether it will or will not help, as some patients apparently are benefited symptomatically, even though it does not cause an increase in the blood count. To a number of patients with a blood count around 3,500,000 and hemoglobin around 70, I have given several transfusions close together with excellent results. This form of therapy is used too little.

The alkalies have a very limited field, usually only helping the type with pseudo-ulcer syndromes and then do not give the brilliant results accomplished by them in the treatment of ulcer.

Dilute hydrochloric acid and pepsin should be given a trial in all cases of achlorhydria and hypo-acidity. It is frequently the only thing which will relieve the patient of digestive symptoms, and strangely enough, some patients with acidity nearly normal will be helped. If small doses do not help, large doses should be tried.

Charcoal, asafoetida, and chlorodyne are indicated in those patients with annoying bloating and distention.

Many methods of attempting to change the bacterial flora have been suggested. In my opinion, intestinal antiseptics and cultures of acidophilus are of little value. Large doses of lactose or lactic acid preparations seem to possess some value in the occasional case. A preparation of sodium ricinolate, called Soricin, is supposed to possess properties similar to castor oil, without the unpleasant features. It seems especially useful in combating distress in the right lower quadrant caused by cecal stasis.

In recent years the vitamins have assumed a major rôle in the therapy of all undernutritional states. It is very seldom that one sees a gross vitamin deficiency, and seldom is there a

vest in a regular support, which obviously should not be prescribed on the diagnosis of visceroptosis alone.

Operations.—Quite a few years ago, surgery was much in vogue in these cases, and in the foreign literature they are still discussing operation for ptosis. In the best of medical circles, however, the surgeons are skeptical and some one has aptly expressed the general consensus by saying that surgery of visceroptosis is vandalism. In addition to operations for correcting visceroptosis, which, as I say, have largely been abandoned, the patient with asthenic indigestion is subject to many other operations, such as appendectomy, cholecystectomy, pelvic operations, etc. These are performed either because of a lack of understanding of the nature of the trouble, or in a vain hope that the patient might improve. The surgeon should have his eyes open, however, for the occasionally definitely demonstrated organic lesion, and also for dilated duodenum, a condition which is common in ptosis. When of only moderate degree this will respond to medical treatment, but occasionally a duodeno-enterostomy is necessary. All dilated duodenums do not give symptoms, however, and the condition should be accompanied by the usual syndrome of pain, vomiting and migraine headaches, if relief is to be expected from operation.

General Considerations.—Lastly, if one is fortunate enough to salvage one of these human wrecks one must stand by ready to detect the first signs of relapse. In other words, it is necessary to keep in fairly close touch with these patients and to give them good advice about daily regulation of their lives. Some regulation along the lines of a definite program works very well. A little time and attention given these patients brings excellent rewards, even though at times the whole problem may be very annoying and discouraging to both physician and patient on account of the time, effort and patience necessary to accomplish good results.

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therapy does not give the same relief. Whole pituitary is sometimes suggested for its stimulating effects, but results are difficult to evaluate. Undoubtedly some disturbance of pituitary function must be a factor in many cases but the problem has not been solved in a therapeutic way.

Exercise and Physical Therapy.—Goldthwaite and the Boston school have been the chief advocates of the importance of exercise, and the correction of postural defects in the asthenic patient. Besides being of very great value, exercise and physiotherapy possess the same psychic value as the various colored lights and inactive electrical therapy of the faith healer. A good physiotherapy department can be of great aid in the management of patients and frequently means the difference between losing the patient entirely and getting a clinical cure. Exercises should be especially directed toward deeper breathing and improving the posture and the tone of the abdominal muscles.

The baths and massage, or baking and massage are excellent for the high-strung type, or the patient with vague aches and pains. Ultraviolet light also is of definite value.

The question of colon irrigations is one that I am not prepared to answer. It must have its benefits, as some patients swear by it and some reputable physicians are enthusiastic, while others are equally critical. Once begun, it seems necessary to keep it up to get relief, and I personally have advised it in but very few cases and in these have suggested only an occasional irrigation. These few patients have had large, atonic colons, and I feel the occasional complete evacuation of the bowel is necessary in order to get the benefit of other measures, directed toward toning up the intestines. I have very grave doubts as to the advisability of colonic irrigations in the patient with an irritable colon and mucous colopathy.

Supports must be prescribed with caution, for they are expensive, and frequently uncomfortable. The patient often refuses to wear one, and the useless corset may become a source of conflict between physician and patients. Some type of bandage support should be tried before having the patient in-

lieves is the result of low-grade infection transferred from neighboring organs.

A routine esophagosopic examination may not be necessary in typical cases of pharyngo-esophageal diverticula, or in cases of traction or deep-seated diverticula which are discovered during a routine gastro-intestinal roentgen examination. But if the sac is atypical and does not adequately explain the history, the diagnosis is not complete without an esophagosopic examination to rule out other possible lesions in the esophagus. Using a thread as a guide eliminates the hazards formerly associated with esophagoscopy in this type of case.

Esophagosopic examination, of course, is not without risk, and the presence of contraindications, such as acute esophageal inflammation, aneurysm, mediastinal tumor, metastases, unusual rigidity or curvature of the spine, necessarily leaves the diagnosis in the hands of a roentgenologist, who, as a consultant, has to interpret his findings in the light of the history, physical examination, laboratory, and throat findings.

The roentgen examination is indicated in all cases of dysphagia. It is free from danger, comparatively simple, and no one questions its value. The thin suspension of barium should always be used first. It will fill a diverticulum which might be missed by the usual thick suspension. In the absence of an obstructive lesion the thick suspension is then used. In case of a doubtful nonobstructing lesion, after the fluoroscopic examination with the patient in all positions including the right and left oblique prone positions during full inspiration, films are made while the patient is swallowing barium as well as after the barium has had time to pass through the esophagus. The only evidence of a small lesion may be a thin coating of barium which adheres to the lesion after the remainder of the esophagus is empty. In the case of an irregular partially obstructing lesion the examination should be repeated after thorough lavage, to make certain that the irregularity is not due to retained food or mucus. In case of questionable esophageal disease, the stomach, particularly the cardiac end, must be examined with the patient in all positions, particularly in the

LESIONS OF THE ESOPHAGUS

E. N. COLLINS

THE team-work of the roentgenologist and the esophagoscopist in the diagnosis of esophageal lesions has become routine procedure. The esophagoscopist wishes to obtain the maximum information possible during the roentgenologist's examination, just as the roentgenologist wishes to confirm his findings by direct inspection through the esophagoscope. The final diagnosis is made either by direct inspection or by biopsy. All will agree with Jackson¹ that all other means by which an early diagnosis of esophageal malignancy can be made (other than by the use of the roentgen examination and esophagoscopy) are inconclusive if not even dangerous.

Because of the similar roentgen findings in various esophageal lesions, it is now realized that an esophagoscopic examination is indicated in practically all cases to determine the cause of the roentgen findings. This includes patients having diaphragmatic hernia and those having lesions at the cardiac orifice of the stomach. It is indicated particularly in all types of obstruction, and in all cases in which carcinoma is suspected, regardless of negative roentgen findings. The fact that an early nonobstructive carcinomatous lesion may give no roentgen evidence of its presence should be emphasized. Also, from the roentgen evidence alone, it may be impossible to differentiate a fairly advanced annular carcinoma or an obstruction from scar tissue with superimposed spasm, from cardiospasm. Mosher² believes that the term "cardiospasm" is a misnomer, that "fibrosis of the terminal portion of the esophagus" is correct, in view of his demonstrations in these cases of fibrosis of the peri-esophageal connective tissue in the crural ring, associated with fibrosis of the musculature of the esophagus which he be-

the cardiac orifice, suggestive of carcinoma without obstruction above this point (Fig. 192). Esophagoscopic examination was advised, but was not done. In view of the history of a similar attack two years before and the high free acidity in the gastric contents, the clinician thought the reported deformity might be



Fig. 192.—Roentgenogram showing filling defect at cardiac orifice of stomach. (Case I.)

due to an atypical gastric ulcer, and so advised medical management for ulcer. There was some improvement.

One month later the roentgen examination revealed a hiatus hernia (Fig. 193) in the region of the filling defect formerly reported which was present only part of the time while the patient was in the Trendelenburg position. In all other positions it was reduced and there was no retention. Above the hernia, however, there was abnormal dilatation, but only at the time the

supine and Trendelenburg positions, if obstruction is not complete in order to detect or exclude the primary lesion in the stomach, or a gastric lesion causing esophageal symptoms.

When an esophagoscopy examination is not going to be done in a case of suspected early carcinoma, and the usual roentgen methods of examination give negative findings, special roentgen methods, such as the one devised by Hickey³ should be used. Soft gelatin bougies containing barium, 3 to 4 cm. long and from 8 to 16 mm. in diameter, are swallowed with water, starting with the smallest size. If one of these plugs sticks, it can be softened and dislodged with a drink of warm water, or the size and contour of the esophagus above the point of constriction can be studied for a moment or so by giving the patient a thin mixture of barium. When the bougie is suspended on a thread it may be raised or lowered where further study is desired. A negative diagnosis can be made if the larger sizes (14 mm. in diameter) pass uninterruptedly through the esophagus.

Carcinoma, cardiospasm, various types of diverticula, obstructions due to diaphragmatic hernia or to scar-tissue narrowing, constitute the majority of lesions affecting the esophageal wall. The following cases either emphasize certain features in the diagnosis of esophageal lesions, or illustrate the rarer esophageal lesions.

Case I.—A man, aged sixty-five, complained that for two months he had had more or less continuous grinding pain in the region of the lower third of the sternum and upper epigastrium, sometimes felt in the back, in the region of the lower thoracic spine. He had lost 15 pounds since the onset of the trouble. The distress was slightly relieved by food and alkalies. The patient stated that he had had a similar attack two years previously when a diagnosis of gastric ulcer was made, and that he recovered completely on medical treatment for ulcer. There was no dysphagia, nausea, vomiting, nor tarry stools.

The Ewald test meal revealed 95 free hydrochloric acid, 115 total acid, and coffee-colored blood. The blood count showed 78 per cent hemoglobin, red cells 4,480,000, white cells 5600. The roentgen examination revealed a filling defect at

roentgenologist (Fig. 194). Atropine, given to physiologic tolerance, relieved the patient's symptoms for the time being.

Six months from the date of entrance the roentgenographic diagnosis was extensive carcinoma of the esophagus, middle



Fig. 194.—Roentgenogram showing carcinoma in middle and lower portions of the esophagus. (Case I.)

and lower third with incomplete obstruction. This was confirmed by esophagoscopic examination the following day.

Although the final outcome in this case would have been no different, an esophagoscopic examination following the initial roentgen examination would have established the correct diagnosis, would have been of considerable prognostic value, would have made repeated roentgen examinations and exploratory

barium was being swallowed. Both roentgen examinations revealed a slight deformity of the duodenal bulb, thought to be due to an old healed ulcer.

One month later exploratory operation was done. No abnormality, other than the hiatus hernia and duodenal ulcer of questionable activity, was found. Posterior gastro-enterostomy



Fig. 193.—Roentgenogram showing hiatus hernia with patient in supine Trendelenburg position. (Case I.)

and fixation of the stomach to the mesentery in the attempt to keep the hiatus hernia permanently reduced, were done. Again the patient's condition improved.

Approximately four months after the first examination the roentgen study revealed a lesion in the middle and lower third of esophagus, associated with partial obstruction and intermittent spasm which was considered as carcinoma by the

be a part of the condition known as simple achlorhydric anemia, the case should not be considered a true example of the syndrome described by Drs. Plummer and Vinson unless the roentgen and esophagoscopy examinations show entirely normal findings.

Case III.—A man, aged forty-seven, had had a chronic productive cough and dysphagia for eight months during which time



Fig. 195.—Roentgenogram of chest showing infiltration, consolidation and cavity formation in right upper lobe. (Case III.)

he had lost 30 pounds. The patient developed the symptoms referable to the lungs and to the esophagus at about the same time. The cough was at first nonproductive but soon after the onset there was considerable purulent sputum, having a foul odor. There had been no hemoptysis or bloody sputum. The dysphagia was limited to difficulty in swallowing solid food at

operation unnecessary, and would have saved the patient considerable inconvenience and expense. In addition to the early suspicion of carcinoma, esophagoscopy was indicated in this case because of the presence of the diaphragmatic hernia. In a recent review of 177 cases, Harrington⁴ emphasizes the fact that "esophagoscopy is advisable in all cases of diaphragmatic hernia."

Case II.—A man, aged sixty, complained of difficulty in swallowing solid foods and weakness which had been present for three months. Solid food seemed to lodge behind the sternum, but he had no difficulty in swallowing liquids. There had been no regurgitation of food and no loss of weight.

The routine examination revealed no significant findings. The blood examination showed a marked microcytic anemia; red cells 4,770,000 with 58 per cent hemoglobin, the volume index was 0.77 and the color index 0.61. There was no free acid in the gastric contents following an Ewald test meal.

Roentgen examination revealed a moderate dilatation of the lower two-thirds of the esophagus, apparently due to spasm at the lower end. A thin suspension of barium passed through the cardiac orifice and the stomach, duodenum, and colon were normal.

Esophagoscopy examination revealed no abnormal findings. A diagnosis of simple achlorhydric anemia, associated with the Plummer-Vinson syndrome⁵ was made. The case was thought to be similar to those discussed by Haden,⁶ a condition which is rarely found in the male sex.

The patient received large doses of iron and five months later, the red cell count was 5,120,000 and the hemoglobin 84 per cent. The size of the red cells had returned to normal, as the volume index was 0.98. The dysphagia also was very much improved, in fact he went several weeks at a time without any difficulty in swallowing. The roentgen examination of the esophagus, however, showed the same moderate degree of cardiospasm.

In discussing the group of cases of dysphagia with anemia it should be emphasized that even though the dysphagia may

Tuberculosis could not be excluded (Fig. 195). The roentgen examination of the esophagus revealed a partial obstruction at the level of the clavicles, with smooth dilatation above this point. The esophagus was displaced to the right at this level, suggesting a traction diverticulum as a result of contraction of fibrous tissue on the outer wall of the esophagus (Fig. 196, A and B).

Esophagoscopy examination showed that at the level of the clavicles there was a small dilated portion of the esophagus. At the distal portion of this dilatation a small pin-point opening could be seen. This opening was dilated, using dilators from a No. 16 to the largest, No. 29. The diagnosis was traction diverticulum of the esophagus.

This case of traction diverticulum due to an inflammatory process adjacent to the esophagus is unusual in that it caused extreme difficulty in swallowing. Three weeks later the obstruction became complete and attempts to pass dilators through the esophagoscope were unsuccessful so that gastrostomy was necessary.

Case IV.—A man, aged fifty-four, had had weakness, vomiting and loss of weight during the last nine months. The vomiting occurred immediately after taking solid foods at first, but had become progressively worse until at the time of entrance he had difficulty in keeping water down. The clinical impression was that he was suffering from carcinoma of the esophagus.

The roentgen examination revealed a diffuse scirrhus type (predominating) of carcinoma of the stomach (simulating linitis plastica or fibromatosis), causing obstruction at the lower end of the esophagus, with smooth dilatation above this point. The capacity of the stomach was reduced to a few teaspoonfuls of barium (Fig. 197).

Esophagoscopy examination revealed a normal mucous membrane down to within 1 centimeter of the cardiac end of the stomach, where it was moderately hyperemic and roughened, but without ulceration. The esophagoscope was passed into the stomach, and just beyond the cardia the mucous membrane was pale, firm, and nodular.

first, food seemed to "stick in the neck" and would often be regurgitated. The condition had become progressively worse until at the time of entrance, swallowing liquids had become difficult.

The patient was pale and emaciated and the temperature was 100 F. The chest examination revealed dullness in the right apex posteriorly. Examinations of the nose, throat, and larynx revealed no abnormality. The blood examination a red

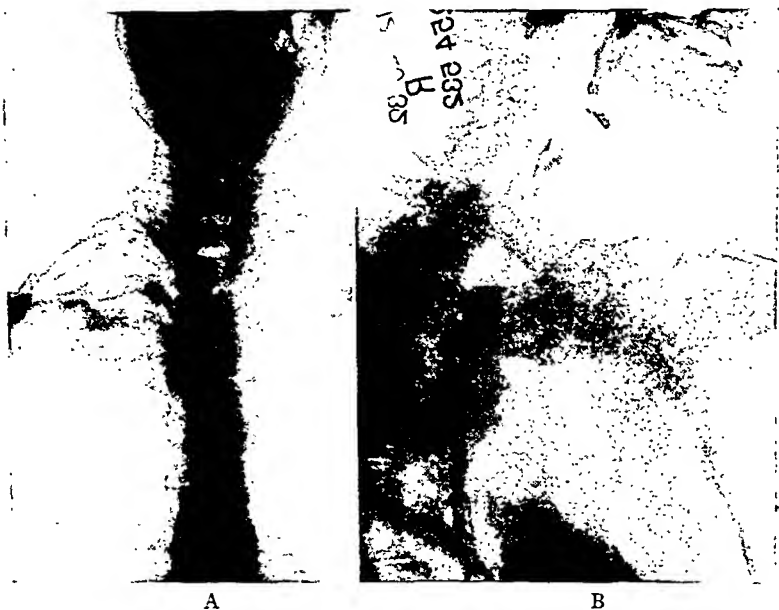


Fig. 196.—Roentgenogram showing traction diverticulum at level of clavicles and displacement of esophagus to the right. (Case III.)

cell count of 3,200,000 with hemoglobin 71 per cent, and white cells 12,000 with 72 per cent neutrophils. Four samples of sputum, each taken on a different day, were negative for tubercle bacilli but contained considerable pus.

Roentgen examinations of the chest showed evidence of exudative infiltration, consolidation, and cavity formation, in the right upper lobe from the first to the third interspaces, adjacent to the mediastinum, interpreted as a lung abscess.

been present for some time, but had become worse lately. The date of onset of this symptom could not be recalled. It consisted of spasmodic attacks of choking while eating, associated with the regurgitation of food (small amounts), eaten at the time. Hoarseness had been present for three months and had followed an acute coryza. The patient had had a tonsillectomy



Fig. 198.—Roentgenogram of chest showing atelectasis of lower left lobe of the lung. (Case V.)

one year previously with a local anesthetic and uneventful recovery. There was no history of fever, sinus infection, pneumonia, or lung abscess, and his weight was stationary. He had a postoperative biliary fistula which drained small amounts of bile and mucus at times. This had been present since the drainage fourteen years ago.

There was some congestion of the larynx. The

A microscopic examination of a specimen removed during esophagoscopy from the lower end of the esophagus showed squamous epithelium on the surface and beneath the epithelium there were multiple nodules of adenocarcinomatous tissue, probably secondary to the carcinoma of the stomach.



Fig. 197.—Roentgenogram showing obstruction at lower end of esophagus caused by carcinoma of the stomach. (Case IV.)

This case is included to emphasize the esophageal symptoms and findings which may be present in carcinoma of the stomach.

Case V.—A physician, aged fifty-nine, complained of a chronic cough, dysphagia and hoarseness. The cough was non-productive and had been present for years. The dysphagia had

Esophagoscopic examination revealed a normal mucous membrane down to within 2 or 3 inches from the cardia. At this point, on the left side, there was a vertical slit in the mucous membrane which opened into the diverticulum. The mucous membrane around this area was of normal color. There was no roughening, ulceration, or malignancy. The esophagoscope was then passed through the cardia and the mucous membrane in this region also had a normal appearance.

This case illustrates an uncommon deep-seated diverticulum, pulsion type, probably of congenital origin, which is causing dysphagia. It is uncommon for a diverticulum of this type to cause pathologic changes in the adjacent lung tissue, but in this case there probably is pressure on the lower left bronchus when the diverticulum is full, resulting in imperfect aeration of the lower left lobe of the lung.

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of the routine examination showed nothing significant except some râles at the left base of the chest.

Roentgenographic examinations showed that the nasal accessory sinuses were normal. The roentgen findings in the chest were interpreted as due to a partial atelectasis of the lower



Fig. 199.—Roentgenogram showing large diverticulum of left lower esophagus. (Case V.)

left lobe of the lung (Fig. 198). Roentgen examination of the esophagus revealed a large diverticulum at the lower end on the left side. This had a short neck, a globular shape, and showed a retention of barium after six hours (Fig. 199). The stomach, duodenum, and colon were normal.

medicine through new methods and improved technic has brought about a change in the operative schedule in hospitals and the frequent necessity for exploratory operation a decade or so ago is no longer prevalent.

The roentgenologic diagnosis of a specific lesion may not always be a solution of the problem, for quite frequently more than one organ may be involved. For example, a patient with a diseased appendix may also have a duodenal ulcer or a gallbladder lesion.

The frequency of gallbladder disease is greater than many suppose and often a patient with cholecystitis, even accompanied by stones, may have no apparent clinical symptoms. Stewart and Leads report 6000 autopsies with gallstones present in 16.4 per cent. In 1000 necropsies, Crump of Vienna found gall stones in 32.5 per cent and cholecystopathy in 60 per cent. Mentzer in 612 routine autopsies found gall stones in 21.6 per cent, cholecystopathy in 66 per cent and in only 15 per cent of the total series of cases was there any clinical evidence of the disease. Routine autopsies show that more than one-half of all persons more than thirty years of age have some cholecystopathy and that gall stones are present in 20 per cent.

In the face of such evidence, great care should be exercised in concluding that the presence of a gallbladder containing stones or a gallbladder found by a cholecystogram to be non-functioning is the cause of the symptoms for which the patient seeks relief. Patients who receive the most satisfactory results from cholecystectomy are those who have had at least one attack of definite biliary colic. Hence unless the patient's symptoms are typical of gallbladder disease, merely the roentgenographic finding of a pathologic gallbladder should not end the search for other disease, even though the symptoms may be confined to the upper right abdominal quadrant. There are several other pathologic conditions in this region which may give symptoms simulating gallbladder disease and the utmost care needs to be exercised in ferreting out the real cause of the trouble.

In our experience, first in importance among such lesions

DIFFERENTIAL DIAGNOSIS IN GALLBLADDER DISEASE

BERNARD H. NICHOLS

ROENTGENOGRAPHY is especially valuable as a diagnostic aid in determining the extent and location of pathologic changes found in the gallbladder and adjacent organs. The sympathetic nervous system, through the superior and inferior mesenteric ganglia, receives fibers from the right kidney and ureter, also from the stomach, duodenum and the right colon and gallbladder. This causes much difficulty in detecting which organ may be responsible for pain situated in this region. As an example, kidney and ureteral lesions are found frequently with pronounced gastro-intestinal symptoms, particularly of nausea and vomiting. Cholecystitis, with or without cholelithiasis, may simulate closely duodenal or gastric ulcer and diseases of these organs may simulate gallbladder disease.

An analysis of a series of 100 cases of kidney tumor seen at the Cleveland Clinic showed that nineteen of the patients, approximately one-fifth, gave no indication by their history and symptoms that their trouble was caused by renal neoplasm. In our series of patients with hydronephrosis, 34 per cent had had previous abdominal operations for relief of symptoms before the exact cause was determined. Other institutions have reported similar statistics.

It is in cases of this type that roentgenology in the hands of a competent roentgenologist manifests itself as a most valuable procedure, for by a process of elimination the correct solution of the problem can usually be made. But the mere taking of roentgenograms often contributes nothing to the diagnosis. This particularly applies to the lesions of the gastro-intestinal tract and often a correct diagnosis can only be made by a skilled fluoroscopist. In many instances the films do not demonstrate the lesion definitely. The development of this branch of

medicine through new methods and improved technic has brought about a change in the operative schedule in hospitals and the frequent necessity for exploratory operation a decade or so ago is no longer prevalent.

The roentgenologic diagnosis of a specific lesion may not always be a solution of the problem, for quite frequently more than one organ may be involved. For example, a patient with a diseased appendix may also have a duodenal ulcer or a gallbladder lesion.

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is hydronephrosis of the right kidney, accompanied by pain and normal urinary findings, except in cases accompanied by ureteral stone, when a few blood cells may be found in the urine. Hydronephrosis frequently is found in young persons who have an aberrant blood vessel obstructing the ureter at the ureteropelvic juncture and should be suspected particularly in young girls who complain of intermittent pain in the upper right abdomen which simulates gallbladder colic but is not accompanied by other gastro-intestinal symptoms. The intravenous administration of one of the iodine salts used in excretory urography, and subsequent radiograms will usually determine the function of the kidney and the dynamics causing the hydro-nephrosis.

The next lesion to suspect is a neoplasm of the right kidney which may occur without hematuria or other abnormal urinary findings in about 20 per cent of all cases in which the predominating symptom is pain with or without a palpable mass. Such a lesion is best diagnosed by a pyelogram made by catheterization of the ureter. Excretory urography does not reveal many of these lesions. The plain stereoscopic examination of the urinary tract which should be done in all questionable right abdominal lesions will show the presence of an abnormal kidney as to size and shape and thereby direct the attention to this organ. Such an examination will determine the presence of lesions located in the lower dorsal and lumbar spine such as a primary or metastatic neoplasm, a fracture, or arthritis.

Case I.—The patient, a man, aged fifty-four years, was first observed at the Cleveland Clinic June 14, 1927. His chief complaint was of aching around the lower chest and back of the neck. One year before admission he had been suffering from severe headaches and a physician had found that he had hypertension, the systolic blood pressure was 190. Urine examination at that time had revealed a trace of albumin and a few hyaline casts. He was treated by dieting and the blood pressure returned to normal, the urine became normal, and the headaches practically disappeared. Although his headaches improved, the aching in the neck, shoulders and around the lower

chest persisted. His discomfort was always worse at night when he was lying down. He had occasional constipation. His teeth and tonsils had been checked as possible foci of infection and had been found normal. His appetite had remained good but he was bothered some with gas and belching. He had no urinary symptoms except nocturia, once or twice.

The patient's temperature was normal. The pulse rate was 90 and the blood pressure was 180 systolic, 110 diastolic. The tongue was coated. The lungs and heart were normal. There was a hard tongue-shaped mass in the right flank that moved freely with respiration. The muscles, bones and joints showed no abnormalities.

The clinical impression from the history and the physical findings was hypertension and questionable Riedel's lobe and arthritis of the spine.

The urine examination showed a faint trace of albumin, an occasional pus cell and 4 to 6 erythrocytes per high power field. The blood studies showed: 4,120,000 red blood cells, 7100 white cells, hemoglobin 85 per cent and urea 36 mg. There was no roentgenographic evidence of arthritis.

A complete genito-urinary investigation was advised because of the questionable mass in the right upper abdominal quadrant. The roentgenogram of the kidneys, ureters and bladder showed a large mass in the right upper quadrant. On cystoscopic examination, the bladder was negative. Catheters passed easily to both renal pelvises. Sodium iodide injected into the right kidney reproduced the patient's pain. The pyelogram showed a large mass in the lower pole of the kidney and the diagnosis was hypernephroma of the right kidney with hydro-nephrosis of the pelvis and cephalic calyx due to pressure of the tumor on the upper part of the ureter. A radiogram of the chest showed no metastases.

A right nephrectomy was performed June 23, 1927. The right kidney was greatly enlarged and nodular by reason of an infiltrating yellowish-colored tumor. The kidney was adherent to the fatty capsule which was very vascular. The diagnosis was hypernephroma.

Arthritis often is suspected from the history and yet x-ray examination of the spine may not show any evidence of pathologic change in the joints but gallstones may be observed on the films, and after cholecystectomy all symptoms of back pain disappear.

Case II.—This patient, a woman, forty-seven years old, presented herself in 1930 and gave the following history. She had had a constant dull aching pain in the right lumbar area since a pelvic operation in 1915. This pain sometimes radiated anteriorly and at other times beneath the shoulder blades. Sudden movements activated the pains. There was no history suggestive of gallstone colic.

Physical examination showed an obese woman with some tenderness over the lumbar and sacral areas. The remainder of the examinations gave normal findings.

The clinical impression from the history and physical findings was arthritis of the spine. A roentgenogram of the spine was secured, which showed no evidence of bone disease but a shadow in the gallbladder area which the roentgenologist considered a gallstone. A cholecystogram was advised and this confirmed the presence of a large gallstone.

A cholecystectomy was performed and the pathologic diagnosis was chronic cholecystitis and cholelithiasis.

This patient was last observed in August, 1933. She was well except for a complaint of some nervousness.

The next thing to consider is renal lithiasis which may cause no abnormal urinary findings. In many instances, the only symptom is pain in the upper right abdomen and back. A large number of these may be apprehended by the plain stereoscopic films, but in about 10 per cent of the cases the kidney stones may not produce a shadow, and a pyelographic examination will be necessary to determine their presence. Many such patients have to carry on for a long time before the correct diagnosis is made, for the physician often relies on the negative findings of the x-ray examination of the kidney.

Stones, stricture or torsion of the right ureter should be considered in conjunction with the right kidney as ureteral ob-

struction may produce hydronephrosis with pain in the upper right abdomen. Frequently, however, the ureteral calculus produces pain that radiates down the ureter to the genitalia and usually careful search will disclose a few blood cells in the urine in these cases. This is of importance and careful microscopic examination should not be neglected in cases of suspected ureteral stone.

Case III.—The patient, a married woman, aged twenty-three years, was first observed at the Cleveland Clinic August 26, 1922. Her chief complaint was of pain in the right upper abdominal quadrant and in the back. Her condition had been diagnosed as cholecystitis and cholelithiasis and she had been treated medically two years for such a condition. Three weeks before coming to the Clinic the gallbladder had been explored and drained. There was no evidence of cholecystopathy or stones and the patient had not been relieved of her symptoms.

The physical examination was essentially negative. The urine examination of a voided specimen was normal except for an occasional pus cell and a slight amount of mucus and a few organisms.

A cystoscopic examination was done. The bladder was normal. A No. 5 ureteral catheter was inserted into the right ureter and this met an obstruction 15 cm. up from the bladder. A slight amount of clear urine was obtained from the right kidney. Sodium iodide was injected and a pyelogram was made. The pyelo-ureterogram showed a stricture of the right ureter with dilatation of the ureter above the stricture.

The final diagnosis was stricture of the right ureter with intermittent hydronephrosis.

Treatment by ureteral dilatation relieved the patient of her symptoms.

The diagnostic roentgenologic procedure in cases of pain in the right upper abdominal quadrant begins with the examination for visible calculi. This is done stereoscopically in order to get the plane of a suspicious shadow and to observe stones lying over the ilium or the lateral processes of the lumbar vertebrae. The next procedure should be excretory urography which is

quite satisfactory in determining obstruction and consequent hydronephrotic change in the kidney. If possible, this study should be made at or near the time of an attack as the ureter may be functioning quite well during the period between attacks. The intravenous urogram will not suffice in all cases and catheterization of the ureter may be necessary to locate the obstruction accurately. These examinations should be attempted before radiography of the gastro-intestinal tract is considered.

The first of the gastro-intestinal examinations is that of the gallbladder itself, before the introduction of any opaque media into the digestive tract. The primary examination, the stereoscopic roentgenogram of the urinary tract, may show suspicious shadows in the gallbladder area.

A plain radiogram of the gallbladder should first be made to confirm the shadows seen on the stereoscopic films of the urinary tract or to show stones not so observed. If shadows of suspicious calculi are observed in both examinations, the gallstones will appear small on cholecystic films because of their close proximity to the films when the patient is in the posterior-anterior position. The presence of calcium in a thickened cholecystic wall may determine the presence of a pathologic gallbladder. After this, a cholecystographic examination should be made. If the gallbladder functions well, stones not previously observed may appear on such films as areas of lesser density in the opaque media. Some observers believe that a fat meal should be given, for this may disclose a stone or small tumor mass in the partially emptied gallbladder that might otherwise go unobserved. The rapidity of emptying of the gallbladder has relatively little clinical significance, for the gallbladder must empty itself many times to concentrate sufficient salt for visualization on the roentgenogram. The significance of nonfilling of the gallbladder can not be evaluated by the roentgenologist from the films alone, for so many factors outside the gallbladder such as hepatitis, a diseased appendix, duodenal ulcer, colitis, may influence function. Hence the roentgenologist is content to report a nonfunctioning gallbladder without comments as to the

presence or absence of any cholecystopathy. If the gallbladder functions well or fairly well, this does not necessarily exclude a diseased condition, for frequently a gallbladder full of stones may have adequate function. The roentgenologist also studies the visualized gallbladder in relation to the duodenum and stomach if a barium meal is introduced while the gallbladder is filled. From this examination one may determine whether or not there are pericholecystic adhesions causing a pressure filling defect in the duodenum or the pyloric end of the stomach. Such filling defects may be observed in the presence of a non-functioning gallbladder which may only be secondary. These facts show how little diagnostic aid can be expected from the direct examination of the gallbladder when opaque stones are absent and when the gallbladder does not function. However, such a finding must be evaluated in relation to the clinical symptoms.

The stomach may next be observed for ulcer or carcinoma, either of which may show symptoms which might be attributed to the gallbladder. These lesions can usually be recognized roentgenographically and their extent and location can also be determined. The duodenum also comes under observation and several lesions of this organ have to be considered in the differential diagnosis of pain in the right abdomen. These are ulcer, diverticulum, congenital or acquired adhesions and dilatation. Any of these may be responsible for symptoms simulating a diseased gallbladder.

Case IV.—This patient, a man, aged sixty-three years, was first observed on November 11, 1932. He complained of stomach trouble of one year's duration and pain in the right side about one to two hours after eating, and food would relieve the pain again for about an hour. Pain awakened him at night and he would have to take milk for relief. Greasy foods aggravated his discomfort. He was well during the summer but in September the pain occurred again and was steadily growing worse. The pain radiated down into the lower abdominal quadrant at times and he had vomited on several occasions. The vomitus did not contain blood. He was not relieved by taking

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ampulla of Vater as a diverticulum. The location of the ampulla and its small size usually suffices to determine this phenomenon. The presence of a dilated duodenum may be observed easily, particularly if the patient is having an attack of symptoms from obstruction or may be elicited by obstructing the duodenum by manual pressure at the ligament of Trietz if examination is done between attacks.

The colon should next be examined for many vague, indefinite gastro-intestinal symptoms are referable to the intestine. Great care should be exercised in attributing symptoms in the upper right abdominal quadrant to this organ in the absence of evidence of definite pathologic changes. Colitis, neoplasms and diverticulosis have been the most frequent conditions causing symptoms in the upper right abdominal quadrant which may be attributed to a pathologic gallbladder. Colitis may be determined by the usual roentgenologic findings of spasticity in the early stages and the smooth unhastrate colon in later stages. Neoplasms are evidenced by their typical filling defects and diverticulosis by the small extra-luminal pockets characteristic of this disease. Diverticuli may remain filled for many days and care should be exercised to exclude the possibility that a previous examination may have caused filled diverticuli in the gallbladder area simulating stones.

Lastly the retrocecal appendix may give symptoms simulating those of cholecystitis. It is the common belief that the presence of appendicitis can not be determined roentgenologically. But this is not true, for a competent roentgenologist can correctly determine an appendiceal lesion more often than the surgeon or the clinician. He has all the clinical advantage of other diagnosticians together with a means of visualization of the region of the appendix when palpation is undertaken. The colon enema or the ingested test meal may not always fill the appendix, but the location of the cecum can always be determined and in about 50 per cent of cases the appendix can be seen. An unrotated cecum, a mobile cecum and a midline cecum all are readily visualized as is any spasm of the ileocolonic sphincter with retention in the lower end of the cecum. All of

food at this time and had begun to lose weight. He had had one severe attack of right upper abdominal quadrant pain associated with jaundice and he had passed clay-colored stools.

Physical examination showed a well-developed man. The temperature, pulse rate, respiration and blood pressure were normal. The tongue was coated. The chest was normal. The heart was slightly enlarged and there were a few extrasystoles. There was some tenderness over the gallbladder and some generalized arteriosclerotic changes.

The impression from the clinical history and the physical findings was cholecystitis and arteriosclerosis.

A combined cholecystographic and gastro-intestinal study showed a functioning gallbladder without evidence of stones and an active duodenal ulcer, nonobstructive.

The patient's referring physician was advised to place him on a rigid Sippy diet. He has not been observed since the diagnosis of active duodenal ulcer was made.

The close proximity of these organs makes physical examination difficult and the roentgenologic findings become of extreme value as a diagnostic aid. Ulcers are most frequently found in the first portion of the duodenum or the bulb and are evidenced by deformity or a definitely filled ulcer crater which may produce obstruction or hypermotility, depending on the extent and activity of the ulcer. Ulcers in the second portion of the duodenum may also be observed by this method of examination. Sometimes the use of atropine or other antispasmodics is a great help in visualization, for some lesions outside the duodenum may produce pylorospasm which will disappear with thorough relaxation. The presence of adhesions may often be apprehended by a constantly deformed bulb without a demonstrable ulcer crater. After the use of an antispasmodic, the high fixation of the second portion of the duodenum may determine the presence of an adhesion band, usually of the congenital type. Such adhesions may cause delay in emptying of the stomach and mild digestive symptoms. Diverticuli show well with proper filling of the duodenum and these may be of clinical significance. Care should be taken not to interpret a dilated

these signs aid definitely in the diagnosis of a diseased appendix. None of these advantages is available to the clinician in a general examination.

All of these factors go to show that the diagnosis of cholecystitis or cholelithiasis is not always easy, for there are so many other lesions that may cause symptoms simulating those of gallbladder disease. Hence a thorough investigation of the urinary tract for infection, stones, hydronephrosis, and tumors has to be made. After that, the digestive tract must be thoroughly investigated by means of various roentgenologic procedures to make certain that the trouble is not situated in the stomach, duodenum, colon or appendix. All these possibilities have to be excluded and considered, together with the cholecystographic findings and clinical history, in making a correct diagnosis in cases of pain in the right upper abdominal quadrant.

dry. The tonsils were cryptic and buried but considered to be normal in the absence of enlarged digastric glands, or history of tonsillitis. The teeth were all vital and in good repair. The lungs were clear and the heart sounds were normal. The pulse rate was 80; the blood pressure 112 systolic, 66 diastolic; the temperature 98.4 F. Abdominal examination showed a normal contour with no visible peristaltic waves, no masses or fluid. The descending colon and sigmoid flexure were spastic and tender. Neither the liver nor spleen could be palpated. The neurologic findings were normal.

Proctoscopic study showed a rosette of inflamed hemorrhoids. The mucosa of the rectum and sigmoid was very red, granular but not ulcerated. There were punctate hemorrhagic spots, especially just inside the internal anal sphincter and most abundant above the great valve of Houston. A culture from the sigmoid area showed nonhemolytic streptococci and gram negative bacilli. Roentgenographic study of the colon showed no abnormality except a lack of haustral markings in the left colon.

The blood count showed 5,140,000 erythrocytes, and 7500 leukocytes with the hemoglobin 97 per cent. The blood sugar was 100 mg. per cent, one-half hour after eating. The Wassermann and Kahn reactions were negative. Gastric analysis revealed free acid, 16 and total acid 48. Examinations of the stool showed no ameba or other parasites.

This patient was advised to take a smooth, nonresidue diet and $\frac{1}{2}$ ounce of malt extract, cod liver oil and iron iodide three times a day. Each night he injected and retained 2 ounces of warm mineral oil in the rectum. In the morning he cleansed the lower bowel with one to two pints of warm normal sodium chloride solution. Additional medication consisted of 10 grains of sodium iodide by mouth three times a day. By the twelfth day an autogenous vaccine had been prepared but his symptoms already had improved considerably. The number of stools had been reduced to three or four a day and they were better formed. At this time a course of vaccine administration was begun. A second proctoscopic examination one month later re-

OBSERVATIONS ON CHRONIC ULCERATIVE COLITIS

JOHN TUCKER

THE proper treatment of chronic ulcerative colitis requires careful diagnostic study and usually, if the disease is chronic, it necessitates a long period of hospital care. Early recognition of the disease, an analysis of its predisposing factors, bacteriologic investigations and complete, painstaking management are all essential to amelioration of symptoms or to recovery from the disease.

Case I. Mild and Early Colitis—Apparent Cure—Remission.—A man, aged twenty-four years, came to the Cleveland Clinic for examination and diagnosis on December 17, 1931. His chief complaint was diarrhea. His illness began about five months prior to this examination, with the sudden onset of severe abdominal cramps and diarrhea. The symptoms were not preceded by any acute illness, but came after a period of nervous strain and long hours at his work. He believed too, that his effort to lose weight by dieting may have been an exciting factor. The stools were often bloody, always watery and accompanied by much tenesmus. Not infrequently he would pass only a small amount of watery or bloody fluid, with an abundance of gas. With the use of a diet and mineral oil he had reduced the evacuations from eight to ten per day to three or four movements. Since the onset of his illness he had lost about 30 pounds.

A survey of his past history did not indicate an unusual tendency to respiratory infections. He had never visited tropical or subtropical countries. In general his health had been unusually good. There is no family history of tuberculosis.

The patient was of the athletic type. His height was $58\frac{1}{4}$ inches and his weight $141\frac{1}{4}$ pounds. The skin and mucosa were of normal color and texture. The tongue was not atrophic or

he had noticed a heavy feeling in the epigastrium, about one-half hour after eating. Some belching of gas occurred but no nausea or vomiting. A few days later he had begun to evacuate four or five watery stools, at times tinged with blood, in twenty-four hours. Rather severe rectal pain had developed. A fistula was discovered and about three weeks before admission had been excised. This operation did not lessen the diarrhea. His appetite had failed and he had lost about 30 pounds. At the time of admission he was very weak and discouraged. The patient had always resided in Ohio, and his health usually had been very good. There was no past history of gastro-intestinal disorders and no chronic cough. His father died of arteriosclerosis and his mother of cancer of the stomach.

The patient was extremely emaciated. His height was 5 feet 10 inches and he weighed 98 pounds. The skin was pale, dry and inelastic, and the tongue was dry, pale and smooth. Dental roentgenograms showed four abscessed teeth, one impacted third molar and considerable gingivitis and caries. The upper respiratory tract was normal and the lungs were clear. The heart sounds were weak, with a pulse rate of 90 and blood pressure 60 systolic, 30 diastolic. The abdomen was scaphoid and thin walled. Peristalsis was not visible and there were no masses, notable tenderness nor muscle spasm. There was no enlargement of the liver or spleen and the patient had no ascites nor edema.

Proctoscopic examination showed a postoperative healing scar in the anal canal, and above this the bowel was empty. It was impossible to introduce the proctoscope more than six inches because of excessive pain resulting from the instrumentation. However, there were no ulcers, scars, bleeding or bloody mucus seen in the rectum and lower sigmoid area.

Roentgenographic studies showed that the gallbladder was nonfunctioning and the stomach normal. There was extensive ulcerative colitis with multiple deformities, the cecum and ascending colon were narrowed and shortened. The ileocecal valve was incompetent with immediate regurgitation into the small bowel during the barium enema. In the chest there was

vealed superficial ulcers in the hemorrhagic and granular areas. The hemorrhoids were more acutely inflamed. These were excised under spinal anesthesia. Following the operation and with continuation of vaccine and other therapy, the patient improved rapidly. A third proctoscopic examination, four months after the first, showed a normal appearing mucosa in the rectum and anus. Further vaccine treatment was discontinued but he was instructed to continue the diet and vitamins. Three months later after dietary indiscretion the diarrhea recurred. This promptly subsided with the use of a freshly prepared vaccine and the smooth, high-vitamin diet.

The patient felt very well until fourteen months afterwards, when he again appeared at the Clinic with his original complaints. In the proctoscopic study the mucosa showed a recurrence of deeper ulceration of the rectum and sigmoid, with a rigid, pipe-like bowel. All of the normal rugae were gone. A smooth, high-vitamin diet and also cod liver oil and yeast extract were administered. This treatment, with the use of a fresh vaccine, caused complete symptomatic relief and after three weeks he had no pain and no diarrhea.

This patient made a satisfactory recovery from the first attack of proctitis. However, he failed to continue the use of a smooth diet with extra vitamins as yeast extract and cod liver oil. He continued to work long hours, which resulted in over-fatigue. These errors in living produced a second and a third exacerbation of his disease. At the present time he has attained a degree of fear and humility which gives some assurance for the future. He thoroughly understands the course he is to pursue and the penalties of disobedience. Valuable time has already been lost in this case and if he fails to take proper care of himself and to report for reexamination at definite intervals, there is a strong probability that he will pass on to the chronic stage of the disease, without future remissions.

Case II. Severe Ulcerative Colitis—Ileostomy—Post-operative Pneumonia.—A man, aged thirty-eight years, was first examined on March 29, 1931. His principal complaint was diarrhea. His illness had begun about three months before when

colon showed that it was considerably shortened, that the lumen was narrowed, and there was absence of haustral markings and considerable deformity about the cecum.

At his third visit to the Clinic on March 9, 1933, nine months after the ileostomy, he had gained 36 pounds. However, he was insistent that something be done to eradicate the artificial anus. Inasmuch as the proctoscopic examination showed a normal rectum and sigmoid mucosa and since his general health was good, and the blood counts and urine were normal, it was decided to anastomose the ileum with the sigmoid. This operation was performed on March 11, 1933. No particular difficulty was met with in this procedure. However, the patient developed pulmonary atelectasis and bronchopneumonia, rapidly grew worse and died on the eighth postoperative day.

At necropsy, the principal findings were chronic ulcerative colitis, the surgical wound (ileosigmoidostomy), bilateral bronchopneumonia, bilateral double ureters, and atrophy and fibrosis of the right suprarenal gland. There was no anatomic evidence of pulmonary, intestinal or renal tuberculosis.

This patient had an extremely severe form of ulcerative colitis which was unusual in that there was very little inflammatory reaction in the rectum or lower sigmoid, while elsewhere in the colon the ulcerations and involvement of the colon wall were most severe. This feature necessitated the utmost care in diagnosis to eliminate amebic dysentery and tuberculosis. Another unusual feature was the inflammatory involvement of the terminal ileum with almost complete obstruction of the lumen. The patient responded very well, at first, to diet and vaccine therapy. Later he again made a remarkable improvement after ileostomy. However, his stubborn insistence that another operation be performed resulted in his death. There is considerable doubt that he would have been as comfortable with restoration of his normal anus, following the ileosigmoidostomy, as he was with the simple ileostomy opening.

Case III. Severe Ulcerative Colitis—Rectovaginal Fistula—Ileostomy.—A married woman, aged forty-six years, was admitted to the Clinic Hospital on December 1, 1932.

evidence of considerable fibrosis extending from the hilum into all lobes, but no exudative lesions could be seen.

The blood count showed 4,442,000 red cells, 14,600 white cells with 71 per cent polymorphonuclears. The hemoglobin was 71 per cent. Blood chlorides were 594 mg. per cent. The Wassermann reaction was negative. Urinalysis showed 1.026 specific gravity, acid reaction, a heavy trace of albumin, and numerous leukocytes and hyaline and granular casts. Gastric analysis showed that the free acid was 34 and the total acid, 54. A culture of nonhemolytic streptococci was obtained from the rectum. Examination of the stools showed pus, 4 plus, mucus, 4 plus, and blood, 4 plus but no ova, parasites or tubercle bacilli were found.

The patient remained in the hospital for three weeks. His treatment consisted of a smooth diet, yeast extract, cod liver oil, iodides, one blood transfusion and an autogenous streptococcic vaccine. All abscessed teeth were removed. He was discharged April 19, 1931, much improved. His appetite was good and he was gaining in weight. The evacuations were one or two formed stools a day.

The patient progressed satisfactorily except for an occasional exacerbation of the diarrhea after dietary indiscretions until March, 1932, when severe cramps and diarrhea recurred. At his second hospital admission, June 20, 1932, he was emaciated (98 pounds), pale and weak. The abdomen was again scaphoid and there was generalized tenderness along the colon. The proctoscopic examination revealed inflammation of the rectal mucosa with one superficial ulcer and a few scars. After preoperative treatment for three weeks an ileostomy was done. The lower six inches of the ileum were found to be inflamed, with a thick and indurated wall. The opening was made a few inches above this area. The patient's convalescence after the operation was stormy, and on two occasions blood transfusions were necessary. However, he was treated with a fresh vaccine, irrigations of the colon with sodium chloride solution, a smooth diet and vitamins.

On January 5, 1933, roentgenographic examination of the

with scarring. The lesions are very painful and begin as a small red papule which she picks at and which eventually enlarge to painful granulomatous lesions. Three types of cutaneous lesions are now present (1) round or oval, pea-sized, depressed or atrophic scars, (2) pea-sized, bright red, excoriated papules and (3) large, irregular, well demarcated, dull red, indolent, slightly indurated plaques the size of a quarter to that of a half dollar. Surfaces show a papillomatous condition with a dirty, slightly adherent, membranous exudate. Other lesions have a clean, ulcerated surface. No pustules are seen. In places there has been some healing with atrophic scarring." The clinical diagnosis was bromide eruption. The patient had no knowledge of bromide medication although she had taken many prescriptions for the diarrhea. The leg ulcers healed rapidly following a large intake of sodium chloride and intravenous injections of sodium chloride solution.

A proctoscopic examination was made under anesthesia and showed severe ulcerations and inflammation of the mucosa, complicated by a rectovaginal fistula. It was impossible to insert the proctoscope higher than the rectum because of the presence of inflammatory edema. Cultures from the rectum showed non-hemolytic streptococci. Examination of the stool showed pus, 3 plus; blood, 1 plus; no amebae; no ova and no tubercle bacilli. A culture from the stool showed nonhemolytic streptococci.

The glucose tolerance test showed a definite diabetic curve, rising to 362 mg. per cent after three hours and 234 mg. per cent at four hours. There was no free acid in the gastric contents and the total acid was 7. Microscopic examination of gastric secretion revealed some food remnants but no lactic acid and no blood. On two occasions the blood cholesterol was 272 and 184 respectively. The specific gravity of the urine was 1.020. Its reaction was acid. There was a trace of albumin and some sugar.

The blood counts showed 3,890,000 erythrocytes with marked anisocytosis and 5400 leucocytes. The hemoglobin was 71 per cent and the differential count was normal.

A roentgenogram of the colon following barium by mouth

Her chief complaints were diarrhea, ulcers on the legs and diabetes. She had been ill since 1914 when there had been a sudden onset of abdominal cramps and diarrhea without any preceding acute infection. The stools soon had begun to contain blood and pus but several examinations failed to reveal amebae. According to her statement, her trouble grew worse steadily and she developed a severe anemia. This caused her to enter a Baltimore hospital where treatment for seven weeks contributed to an amelioration of her symptoms and a gain in weight of 35 pounds. In 1925 she wintered in Florida and Cuba, but had no diarrhea. During the year of 1927, while in Oklahoma, she developed a severe attack of hemorrhoids which was followed by a recurrence of the diarrhea. An anal stricture followed a hemorrhoidectomy operation.

In 1929 she was treated for five weeks at the Johns Hopkins Hospital. She improved on proper therapy but declined to submit to an ileostomy. During the year 1932 she was very uncomfortable on account of the diarrhea. The stools increased in frequency to ten to fourteen each day. Three blood transfusions were required to combat the secondary anemia. In August, 1932, she developed several ulcers on her legs. These lesions resisted ordinary treatment. At that time it was discovered that she had a mild diabetes which appeared to be responsible for the chronicity of the ulcers. About a week before she entered the Clinic Hospital, it was noticed that fecal material was coming from her vaginal orifice.

A physical examination revealed that the patient was extremely emaciated and pale. She weighed 82 pounds and her height was 5 feet, 5 inches. The blood pressure was 126 systolic, 70 diastolic; the pulse rate, 80 and the temperature was 99.6 F. The left eye was reddened by a mild iritis. The tongue was pale and smooth. The abdomen showed a moderate distention and generalized tenderness.

The dermatologic report by Dr. Netherton was as follows: "The patient shows scars and ulcers on the legs. These appeared in August, 1932, after she had been picking blackberries. She has continued to develop new lesions as the older lesions heal

tion with salt solution caused a spontaneous healing of the fistula. However, the colon has been so badly narrowed, shortened and scarred that the ileostomy must remain as a permanent anus. The anemia now presents an important problem. Is it the result of toxic absorption from the colon or an inadequate intake or absorption of iron? What part does the diabetes play in her problem?

It is obvious that the most conservative measures would be to give an anti-anemic, diabetic diet with adequate dosage of insulin and a maximum dosage of iron. This could be continued for several months. One would attempt a colectomy only in the event of failure in the medical management. It is difficult to estimate the influence of the colon as a focus of infection. However, the high blood sedimentation rate and the anemia would give a strong indication that infection is still active.

DISCUSSION

Most of the patients with chronic ulcerative colitis have received indifferent as well as unintelligent care during the early stages of the disease. This occurred in Case II herein reported, but not in Case III. In the latter instance the patient was cared for in two very excellent institutions, but in spite of this, developed a rectovaginal fistula. For one reason or another, she had not been properly instructed regarding her disease. Remission of symptoms was interpreted as a cure, with the result that each exacerbation became successively more severe. If the most highly satisfactory results are to be obtained in the treatment of ulcerative colitis, the living habits of the patients must be modified early in the course of the disease. This procedure is used in the modern care of tuberculosis, diabetes, peptic ulcer and in many other types of chronic diseases in which there are cycles of exacerbations and remissions. The probability of a complete cure is excellent in the first case if the patient will take his problem seriously enough. Should he become incautious in his diet and work, or should he continue to violate the rules necessary to good health, he will, most likely, have the misfortune to become a chronic invalid.

showed that most of the colon was fairly well filled in six hours and showed definite evidence of generalized ulcerative colitis.

Following treatment for two weeks with a smooth diabetic diet, insulin and autogenous vaccine, the patient was referred to the surgical service for an ileostomy. This was performed by Dr. Crile on December 22, 1932. The postoperative course was very satisfactory and the patient made rapid improvement with the use of the vaccine, cod liver oil, vitamin B, diabetic management and irrigation of the colon. She was discharged from the hospital on January 14, 1933, and returned for study on June 8th.

A second proctoscopic examination under gas anesthesia showed marked contraction of the lumen of the rectum and lower sigmoid. The mucosa was greatly thickened and red, with absence of normal rugae and considerable pus was present. Roentgenographic study of the colon showed that it was very short, very narrow, rigid and showed no haustral markings. It filled instantly with a capacity of only four ounces. At this visit, the blood count showed 4,280,000 red cells, 5700 white cells, 78 per cent hemoglobin and a normal differential count. The urine was normal.

The patient had gained 35 pounds and felt very well. She was suffering no abdominal distress and the ileostomy functioned satisfactorily.

She returned to the hospital again on October 3, 1933, and is now under observation. Aside from pallor of the skin, she looks quite well. Her blood count is 3,800,000 erythrocytes, 5200 leukocytes and 63 per cent hemoglobin. The fasting blood sugar is 241 mg. per cent and the urine contains 4 plus sugar. The blood sedimentation rate was 58 mm. the first hour. The rectovaginal fistula is healed and the ileostomy still functions satisfactorily.

This case of severe ulcerative colitis with several periods of remission followed by exacerbation finally resulted in a rectovaginal fistula. This unusual complication of the disease necessitated an ileostomy. This operation produced physiologic rest for the colon, which together with the daily cleansing by irriga-



The excellent magazine articles and monographs on chronic ulcerative colitis, which have appeared in recent literature, emphasize the importance of the streptococcus or organism of Bargaen as well as the prevalence of infective foci in the etiology of this disease.

A word might be said with regard to the type of vaccine to be used in these cases. Formerly, in the treatment of chronic ulcerative colitis, an effort was made to isolate, if possible, the diplococcus of Bargaen. However, it was soon learned that a vaccine made from the first growth of a polyvalent culture and which almost always contained the nonhemolytic streptococcus, would give more satisfactory results than a vaccine made from subcultured growths. This experience has led to the conclusion that the important organism is the streptococcus, whether it conforms to Bargaen's requirements or not. Likewise in our experience, subcultured growths have not produced vaccines of a potency equal to those made from primary broth cultures.

The rationale of vitamin feeding in our treatment is borne out by the excellent researches of McCarrison, Cramer, Grant and others who have demonstrated that ulcers will develop in the colons of birds, monkeys and guinea pigs when the diet is deficient in vitamins. The mechanism of the ulcer formation is discussed in the monographs published by these authors.

Many of the authors have failed to stress the need of frequent follow-up observations, such as has been the established procedure in many chronic ailments. Many patients with mild proctitis and sigmoiditis probably get well eventually without any specific form of treatment and some do not have recurrence of diarrhea and tenesmus. However, too many such patients are treated symptomatically in the earlier stages to the patient's disadvantage. Every such instance should be regarded as a potential case of chronic ulcerative colitis. It is the duty of the physician to prevent development of the late stages in the light of present knowledge of this most serious disease.

Certain drugs which cause vasoconstriction may produce albuminuria as has been demonstrated by the injection of epinephrine and ephedrine. The emotion and activity produced by fright and pain has caused protein to appear in the urine of cats. Compression of the renal vessels has resulted in albuminuria even when the pressure has been insufficient or too fleeting to cause any demonstrable kidney damage. The regular appearance of albumin in the urine during congestive heart failure further suggests the rôle which circulatory disturbances may play in producing proteinuria, as does also the proteinuria following a cold bath in susceptible persons.

Temporary proteinuria has been reported in cases of cerebral hemorrhage and also in cases of severe injury with shock, even when the kidneys were uninjured. The basis of this must lie in a renal circulatory change.

The albuminuria accompanying febrile illnesses is usually described as being of toxic origin although the nature of the toxic products is not clearly understood. It may be in these cases that there is accompanying renal damage which clears up with the disappearance of the inciting condition.

Finally, it has been demonstrated by Longcope and Rackemann that in sensitive persons, the injection of infinitesimal amounts of the specific protein will induce a proteinuria of allergic origin.

It is obvious therefore that proteinuria exists in a variety of conditions unaccompanied by demonstrable evidences of renal damage and usually associated with circulatory disturbances of the kidney.

Proteinuria is a practically constant accompaniment of renal damage and its presence must immediately suggest such a diagnosis unless it can clearly be excluded. In acute hemorrhagic Bright's disease, the initial proteinuria varies according to the severity of the disease. With improvement it decreases and with recovery it disappears. It may in some cases persist long after the patient has apparently recovered his health completely. In those cases which represent the chronic active stage of the disease, proteinuria persists and increases with any

THE CLINICAL SIGNIFICANCE OF ALBUMINURIA

R. H. McDONALD

THE demonstration of albuminuria by the common methods of testing the urine introduces immediately the question of its significance in relation to diagnosis, prognosis and treatment. Ruling out immediately the suppurative lesions of the genito-urinary tract in which the albuminuria is associated with gross amounts of pus and other evidences of bacterial invasion, there still remains a great group of cases in which the question arises as to what importance to attribute to this finding.

One may properly enlarge this subject from a consideration of albuminuria to the subject of proteinuria inasmuch as the substance precipitated usually is not wholly albumin but contains in varying amounts the other proteins of the blood plasma, globulin and fibrinogen and when there is destruction of red blood cells, also, hemoglobin.

It has been commonly stated that the normal urine contains no protein, but clinical observation supports the view that in a variety of cases, there is proteinuria which is non-nephritic and benign and significant of no renal damage.

Hugh McLean in a study of 60,000 apparently healthy recruits found an incidence of albuminuria in 5 per cent in early morning specimens. After exercise it was demonstrated in from 7 to 14 per cent and this effect of exercise in certain individuals has been repeatedly demonstrated by other observers.

Orthostatic albuminuria, or the appearance of albumin in the urine on the assumption of the erect posture is frequently seen in adolescents, particularly those who have grown rapidly and are of a lean, visceroptotic type and have evidences of a general cardiac and vasomotor irritability, frequently with low blood pressure.

though a few hyaline casts with some red or white blood cells may be present. In the true nephritides there is usually a suggestive history of kidney involvement, frequently associated hypertension and a persistent proteinuria with abundant evidence of renal disease as shown by erythrocytes, leukocytes and casts in the urine, while the renal function tests show varying degrees of reduction. Any patient having proteinuria should have careful study and generally the diagnosis of benign proteinuria can only be made after repeated observations.

It has been mentioned above that the major fraction of urinary protein is albumin with lesser amounts of globulin and traces of fibrinogen and hemoglobin. The ratio of albumin to globulin is usually high in the benign proteinurias, at least 10: 1, and also is high in acute nephritides and nephroses, decreasing somewhat with the progression of the disease so that a decreased albumin-globulin ratio of the urine is of some significance in prognosis.

It is, of course, probable that these urinary proteins represent chiefly proteins of the serum which have escaped because the capillary endothelium and the renal epithelium have been rendered unusually permeable by the effect of circulatory disturbances, disease or some other factor. In nephritis a small amount must represent the products of disintegration of renal epithelium but this can hardly make up any considerable quantity of the relatively great amount excreted in hemorrhagic and degenerative nephritis, and leaves entirely unexplained the benign proteinurias.

Proteinuria represents a loss of substances essential to the body and consequently, if prolonged, results in a measurable loss of serum proteins which reaches its maximum in the degenerative forms of renal lesions. The total albumin in the blood of an adult weighing 70 kilograms averages 140 grams. A loss of 10 to 20 grams daily in the urine without replacement would reduce the serum albumin content by one-half in four to seven days. Replacement by synthesis at such a rate may well approach the limit of the body's powers and if continued, would result in a reduction of serum protein. There are other factors

exacerbation of the renal lesion. If renal insufficiency and hyposthenuria appear, the proteinuria usually diminishes apparently as a result of the diminution of renal functioning elements.

Maximum proteinuria is seen in the degenerative types of Bright's disease. A massive proteinuria is a distinguishing feature of this type and may reach a daily output of 20 grams.

In the arteriosclerotic types of renal lesions there may be only trifling amounts of albumin increasing as the vascular damage to the kidney increases, especially if intercurrent infection, heart failure or the imposition of an acute nephritis occurs.

Mention should also be made of the presence in certain cases of a special proteinuria which bears the name of its discoverer, Bence-Jones, who first observed it in a patient with multiple myelomata. It is distinguished by the fact that it is precipitated by moderate heat 60–65 C. but redissolves as the boiling point is reached. It is found in patients with disease of the bone marrow or blood forming organs and has been described in cases of chloroma, tuberculous disease of the bone, secondary carcinoma of the marrow and leukemia. It has been reported in a case of Hodgkin's disease, in lymphosarcoma of the colon, in myxedema and nephritis. Its exact nature is unknown, the best hypothesis being that it is the specifically elaborated product of the tumor or of the diseased organ.

The differentiation of these varied conditions which may be responsible for proteinuria is frequently very complicated. The clinical history, the physical examination and the laboratory findings, especially the microscopic study of the urinary sediment and studies of renal function, notably the urea clearance test, must all be utilized. In general the benign proteinurias mentioned above give a negative history of antecedent renal disease and clinically show none of the accompanying signs of kidney degeneration. The proteinuria is variable and may be related to some external factors such as chilling, exercise, posture or allergy. The urine contains, besides the albumin, little evidence of renal damage such as erythrocytes or casts, al-

The development of edema in chronic hemorrhagic renal disease suggests the necessity of increased protein intake and is the basis for the Epstein high-protein diet which has been successfully used in the treatment of degenerative Bright's disease. The necessity for adequate protein intake throughout the course of arteriosclerotic renal disease is also made evident by the urinary protein loss. In general, the conception now exists that in the presence of steady loss of urinary protein which characterizes Bright's disease, protein feeding must be adequate unless there is evidence of renal insufficiency and increased blood nitrogen. The application of this principle has resulted in considerable improvement in patients who have previously been kept on protein-free diets.

SUMMARY

1. Proteinuria may under certain conditions be benign.
2. Generally it is indicative of renal damage and represents a loss to the body which may be the basis of symptoms and which should be replaced by adequate protein feeding.

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in the serum protein deficit characteristic of severe renal disease. Hydremia occurs and dilution of the plasma gives qualitative reduction. Malnutrition is also a large factor and may be due to the anorexia and digestive disturbances accompanying renal disease or frequently to protein starvation, the result of misguided therapy.

The average normal plasma protein content is 7 grams per cent of which 4.44 grams per cent is albumin, and 2.58 globulin with a specific gravity of 1.027. The albumin-globulin ratio of the serum therefore is 1.72. Decrease of plasma protein below a total of 5.5 per cent or albumin below 2.5 per cent is regularly followed by edema. The specific gravity of plasma at this critical level is 1.022.

The reason for the development of edema at this level is as follows. The diffusible portion of the blood is held within the capillaries because of the osmotic pressure exerted by the plasma proteins as demonstrated by Starling. Reduction of proteins to such a level that the osmotic pressure exerted by them is less than the normal pressure within the capillaries results in edema, although there are other factors which enter into its production. In acute hemorrhagic Bright's disease there is frequently edema due to increased capillary permeability of toxic origin. The chloride intake and content of the serum is also a factor, and in late stages edema may result from myocardial failure. The greatest factor, however, in edema in renal disease is undoubtedly plasma protein deficit resulting from proteinuria.

The degree of proteinuria in itself is not a safe indicator for treatment but should suggest serum protein studies from which indications for therapy may be judged. The protein loss must suggest the necessity for its replacement and in recent years this conception of the treatment of renal disease has become well established. In acute hemorrhagic renal disease, the protein must be restored in the diet so that within a period of three weeks, an adequate amount of protein is being ingested. However, immediately after the acute symptoms subside, protein must be restored in the diet so that within a period of three weeks, an adequate amount of protein is being ingested.

binning power and for serum protein content, may give valuable information as to the type and severity of the lesion.

CLASSIFICATION OF BRIGHT'S DISEASE (Addis)

- | | | | |
|-----------------|---------|--------|----------|
| I. Hemorrhagic: | Acute | Latent | Healed |
| | Chronic | Active | Terminal |
- II. Degenerative:
1. Cryptic (lipoid nephrosis).
 2. Poisons of known composition.
 3. Pregnancy toxemias.
 4. Toxemia associated with general infections.
 5. Toxemia associated with focal infections.
 6. Toxemia associated with mixed infections.
- III. Arteriosclerotic:
1. Benign.
 2. Malignant.

I. Hemorrhagic Bright's disease is characterized by the presence in the urine of red blood cells; in this type erythrocytes are always present if carefully searched for in twelve-hour dry specimens. This condition is the result of streptococcal infection and frequently develops subsequent to infections of the throat, erysipelas or scarlet fever. The initial symptoms are related to partial or temporary complete renal insufficiency as a result of the renal congestion and edema. The severity of symptoms varies considerably. At times the onset is so insidious that the initial symptoms are overlooked; at other times, the renal lesion may be severe enough to induce uremic symptoms. In the usual case, there is general malaise, headache and gastro-intestinal symptoms. Urinary excretion is decreased in amount, and has increased color and specific gravity. Urinalysis shows heavy albuminuria, and on microscopic examination there are very numerous red blood cells, many white blood cells, granular and hyaline casts and epithelial cells.

Physical examination usually reveals some increase in blood pressure and some edema, especially noted in the loose areolar tissue of the orbit. Some degree of anemia is usually present and serum protein studies may reveal a considerable deficit in the more severe cases. After a few weeks in favorable cases the acute symptoms subside and improvement occurs with

CLINICAL TYPES OF BRIGHT'S DISEASE

R. H. McDONALD

FOLLOWING the example of Addis, the term "Bright's disease" is used to include the nonsuppurative bilateral kidney lesions usually grouped under the term nephritis. Inasmuch as this latter term is regarded as indicative of an inflammatory lesion, the term "Bright's disease" is used because it is wider in application and includes those lesions of the kidney which are primarily degenerative or vascular in origin as well as of the inflammatory type.

The classification of Addis as modified by Van Slyke is used because it is entirely a clinical classification based upon history, physical examination and laboratory procedures, especially, careful study of the urine. It is essentially a classification into which the living patient may be fitted without waiting for the pathologic diagnosis, and, as such, forms an excellent background for the diagnosis and rational treatment of the patient by the practitioner who is concerned with the practical problem of his care. A careful history, physical examination and study of the urine will enable one to classify the great majority of cases of renal disease in one of these groups. Difficulty may be experienced in some instances because of complicating factors and because combinations of these forms exist. In addition to the usual history and physical examination, renal investigation should include careful microscopic study of urinary sediments obtained from specimens collected after a twelve-hour period without liquid. Various tests of the renal function are employed; in my experience the most useful undoubtedly is the urea clearance test of Van Slyke. Finally study of the blood chemistry for the urea, uric acid, creatinin, and nonprotein-nitrogen content, for cholesterol, chlorides, carbon dioxide com-

of this stage varies from a few weeks to two years. There is gradual increase in the nitrogen of the blood, or in the presence of an acute infection, nitrogen accumulation is rapid, terminating in uremia.

The following case history illustrates the course of a patient who falls in group I:

Case I.—A boy, aged sixteen years, was seen in the Cleveland Clinic first on August 6, 1928. He had had a mild attack of scarlet fever at the age of two and one-half years. When he was eight years of age, he had had a severe infection of the scalp which necessitated surgical drainage. At that time albumin was reported in the urine. Puffiness of the face and recurrent edema of the extremities had developed during the two years preceding his first examination at the Clinic. He had been on a restricted protein diet for three years. The patient complained of fatigue, frequent headaches and some blurring of vision.

Examination showed a fairly well-nourished boy, whose pulse rate was 84, the temperature 98.4 F., and the blood pressure 115 systolic, 80 diastolic. There was definite puffiness about the eyes and some edema of the feet and ankles. The retinal examination showed a diffuse albuminuric retinitis. The heart was not enlarged and a special neurologic examination showed no abnormalities. Urinalysis showed an acid urine with the specific gravity 1.010, no sugar and a slight amount of albumin. The microscopic examination of the urine showed persistently from 8 to 10 red blood cells per high power field and rare granular casts. Quantitative urinary protein studies showed 3 Gm. output in twenty-four hours. The phenolsulphonphthalein test showed 20 per cent output in the first hour and 15 per cent in the second hour. The red blood count was 4,670,000, the white blood count 10,000 and the hemoglobin 91 per cent. Blood sugar was 107 mg. five hours after food, the blood urea 15 mg., uric acid, 2.8 mg., creatinin, 1.2 mg., and chlorides 594 mg. The Mosenthal test showed that the night specimen of urine was 500 cc. and had a specific gravity of 1.012. The specific gravity of two-hour dry specimens varied from 1.006

increased urinary output and return to normal blood pressure. The amount of blood in the urine also decreases.

Following the acute phase the patient may pass into a latent or symptom-free phase in which all subjective signs and symptoms pass but in which urinary study reveals the continued presence of albuminuria and microscopic study of concentrated specimens of urine will reveal the presence of erythrocytes. Urea clearance tests at this stage usually show some decrease of renal function which may persist; this evidently is the result of some renal parenchymal destruction. The duration of the latent phase may be for several years and its passage into the healed state in cases with favorable outcome occurs without obvious clinical sign.

In less favorable cases the disease passes either directly from the initial phase or after a latent period of variable duration, into the active chronic stage. The patient remains ill, the nutrition is usually subnormal and anemia is present, and there may be edema. There is usually some elevation of blood pressure. Urinalysis reveals a persisting albuminuria and hematuria with signs of renal degeneration, epithelial cells and casts. There is frequently an associated plasma protein deficit with high plasma fat and cholesterol content. Urea clearance tests usually show progressive loss of renal function and almost invariably the clinical course in such a patient is steadily downward.

The differentiation between the chronic active and terminal stage is not apparent clinically. It has been set arbitrarily by Van Slyke at the urea clearance level of 20 per cent of normal. There are increasing symptoms of illness and hypertension is the rule. Generally the edema tends to disappear or lessen and the patient tends to develop the uremic type of symptoms as renal function falls below the level at which adequate excretion of nitrogen is possible. Generally the urinary signs persist, and hematuria is still present to some degree. The amount of albumin and casts is less than in the chronic active stage and there frequently is an increase in the plasma protein content at this stage with resultant lessening of the edema. The duration

in this type of Bright's disease. Plasma protein deficits are the rule and are accompanied by increased fat and cholesterol content. Anemia is not a feature of the early phases of the condition.

The clinical course of this condition is variable. According to some authors, the outlook is better than in the hemorrhagic types, with recovery in some cases. This would appear to be more likely in children. In adults, in our experience, such cases have invariably shown progressive degeneration with ultimate evidence of renal failure or the patients have succumbed to intercurrent infection to which they are peculiarly susceptible.

Differentiation between the chronic active hemorrhagic phase of the hemorrhagic type and the degenerative type may be difficult. Edema, heavy proteinuria with microscopic evidence of renal degeneration and plasma protein deficit are seen in both. The history of a sudden onset, of hypertension at some stage of the disease and the presence of hematuria suggests the hemorrhagic type. Hypertension and hematuria may be lacking at some periods in chronic hemorrhagic disease, and then the differentiation is difficult. Generally the edema and proteinuria are more massive in the degenerative type and nitrogen retention occurs later in the course of the disease than in the hemorrhagic type.

Case II.—A married woman, aged thirty-two years, was admitted to the Cleveland Clinic on May 23, 1932. She had had a child on March 20, 1932. One week following the delivery, which was normal, the patient had contracted influenza and during this attack had developed generalized edema which had been variable, but never disappeared completely. Ten days before admission she had developed ascites. The patient had been confined to bed on a very low protein diet and had become very pale.

There was no previous history of renal disease. The patient had had scarlet fever in childhood, measles, whooping cough, mumps, chickenpox, an attack of pleurisy in adult life and influenza as noted above.

to 1.020. The blood Wassermann and Kahn reactions were negative.

The patient returned August 2, 1933, complaining of rather severe headache, general lack of energy and moderate edema of transient nature. Examination showed a marked degree of pallor. The pulse rate was 84 and the blood pressure 142 systolic, 90 diastolic. There was marked albuminuric retinitis and moderate cardiac enlargement. The neurologic examination revealed nothing of significance. Urinalysis showed albuminuria, graded 4 + with many red blood cells, a few white blood cells and granular casts on microscopic examination. The blood count showed 2,010,000 red blood cells, 6150 white blood cells and 39 per cent hemoglobin. The blood urea was 240 mg., creatinin 10.4 mg., and the blood sugar was 132 mg., four hours after food. The urea clearance test showed 5 per cent function in the first hour and 6 per cent in the second.

This patient is at present in the terminal phase of hemorrhagic Bright's disease. The sudden onset of the renal condition following infection is typical and the eight-year course has included an initial, latent, active chronic and terminal stage.

II. Degenerative Bright's disease results from a variety of intoxications and includes some cases in which no obvious cause can be determined. These latter are the *cryptic* cases, according to Addis' classification and correspond to the *genuine* cases of Volhard and Fahr. They are distinguished by the finding of doubly refractile bodies in the urine. Degenerative Bright's disease has been seen following intoxication with the heavy metals, the toxemias of pregnancy and also associated with general, focal and mixed infections.

Clinically the condition may persist for long periods without other symptoms than gradual deterioration of health of insidious character. The development of edema is a striking feature and usually a persistent characteristic of the condition. Hypertension is absent. Urinalysis reveals massive proteinuria and microscopically much evidence of renal degeneration in epithelial cells and casts of all types. Hematuria is rarely seen

mg., urea 30 mg., creatinin 0.9 mg. and chlorides 517 mg. per cent.

On January 24, 1933, the generalized edema had disappeared but the patient did not feel so well as before. Examination showed some puffiness about the eyes; otherwise the findings were the same. Urinalysis showed albumin 2 to 3 + with numerous hyaline and granular casts and many epithelial cells. The urea clearance showed 10 per cent the first hour and 29 per cent in the second hour. Total serum proteins were 6.25 per cent, albumin 1.77 and globulin 4.48. Total urinary protein was 9.8 grams in twenty-four hours. The blood urea was 78 mg., creatinin 1.6 mg., and cholesterol 158 mg. The red blood cells numbered 3,150,000, white blood cells, 2450 and the hemoglobin, 55 per cent. During her stay in the hospital the patient ran a slight fever and complained of sore throat. Smears from the throat yielded a nonhemolytic streptococcus. During the hospital stay, the patient's course was persistently downward. The patient had fever with the temperature as high as 104 F. The pulse rate increased to 120, the patient showed symptoms of severe toxemia and developed blotchy purpuric spots. She grew worse steadily, and died, apparently of uremia.

The autopsy showed a marked degenerative lesion of the kidneys, and microscopic sections showed generalized hyaline degeneration of the tubular epithelium in both the cortex and medulla.

III. Arteriosclerotic Bright's disease occurs concurrently with general vascular thickening and is thus only part of a general vascular disease. Frequently the vascular changes in the kidney are insufficient to affect renal function to any degree while circulatory change in other organs commands attention. Frequently gradually progressive degeneration of vascular origin may have been present for many years without renal symptoms and often the patient dies as a result of vascular accidents in other parts of the body. However, in some cases, progressive renal degeneration proceeds to the stage where symptoms occur.

Examination showed a well-developed woman, not acutely ill, showing generalized edema and apparent anemia. The pulse rate was 66, the temperature 97 F. and the blood pressure was 112 systolic, 74 diastolic. Pulmonary examination showed a few crepitations at each base. The heart was of normal size and the beats were regular. The abdomen was distended with fluid; there were no palpable masses. There was marked pitting edema of both extremities. Neurologic examination yielded no information of significance. The pelvic examination showed the uterus to be of normal size.

The urine was acid in reaction and had a specific gravity of 1.025 with albumin graded 4 +. The microscopic examination showed an occasional red blood cell per high power field, 8 to 10 white blood cells per high power field, very numerous hyaline casts, many granular casts and epithelial cells. The red blood count was 4,300,000, white blood count 5600 and hemoglobin 91 per cent. The blood sugar was 81 mg. per 100 cc., one and one-half hours after food, urea 27 mg., uric acid 2.4 mg., creatinin 1.0 mg. The blood Wassermann and Kahn tests were negative. Total serum proteins were 3.93 per cent, serum albumin 1.08 per cent and serum globulin 2.85 per cent. The blood cholesterol was 500 mg. The urea clearance test showed 43 per cent in the first hour and 51 per cent in the second hour. The phenolsulphonphthalein test showed 70 per cent in the first hour and 10 per cent in the second hour. The blood culture was negative. The basal metabolic rate was minus 20 per cent.

A high protein diet and thyroid extract were given to the patient and the fluid intake was restricted to 1200 cc. daily. A blood transfusion was administered and the abscessed teeth were removed. One week after her admission, the serum protein had risen to a total of 5.25 per cent; the albumin was 1.35 and the globulin, 3.90.

The patient was seen again on August 16, 1932. Generalized edema still was present and the urinalysis was essentially the same. The total serum proteins were 4.16; the albumin, 1.22 and globulin, 2.94. Cholesterol in the blood measured 309

within the past three years. Otherwise his health had been apparently normal.

The patient's pulse rate was 116, the temperature 99.2 F., and blood pressure 240 systolic, 160 diastolic. Retinal examination showed marked vascular sclerosis but no exudates or hemorrhages. One area of chorioretinitis was present in the left eye. Gross cardiac enlargement was present without any signs of myocardial failure. There was moderate diffuse vascular thickening.

Urinalysis showed acid reaction, specific gravity, 1.010, albumin 1 + and no sugar. The microscopic examination showed a few red blood cells, an occasional white blood cell and rare granular and hyaline casts. The urea clearance was 50 per cent in the first hour and 57 per cent in the second hour. The blood urea was 27 mg., uric acid 4.3 mg., and the creatinin 1.0 mg. per cent. The blood Wassermann and Kahn tests were negative. The blood count showed 4,750,000 red blood cells, 8500 white blood cells and 97 per cent hemoglobin.

The patient was readmitted to the hospital on September 22, 1931, in coma. Relatives said that he had become increasingly weaker in the past three months. Five days before admission some difficulty with speech had been noted. Since then there has been an increasing loss of reason and orientation culminating in complete stupor.

The patient's temperature was 102, the pulse rate 120 and the blood pressure was 200 systolic, 130 diastolic. Neurologic examination showed no evidence of lesion in the pyramidal tract. The spinal puncture showed entirely normal fluid. The pressure was 70 mm. of water. The blood urea was 87 mg. per 100 cc. The urea clearance gave a value of 14 per cent in the first hour. Urinalysis showed albumin 2 +, and many granular and hyaline casts.

The patient's course was progressively downward. Death resulted five days later, apparently from a vascular rupture in the left frontal lobe.

This history illustrates the rapid development of vascular disease, discovered originally during an examination of the pa-

Such patients usually present themselves in a terminal stage on account of the insidious nature of the condition.

The blood pressure in these cases is always elevated, especially the diastolic. A systolic pressure of 200 to 250 mm., and a diastolic pressure over 120, frequently are seen. Hypertension often is discovered only on routine examination but may produce symptoms of headache and dizziness. Urinalysis reveals small amounts of albumin, at times none. As the disease progresses, the urinary signs become more marked, but throughout the course the urinary signs never approach those seen in hemorrhagic or degenerative kidney disease. Hematuria may be seen but not as a constant feature. Plasma protein deficiency is not seen except in severe terminal phases. Anemia is slight. Edema, when present, is of cardiac origin. Urea clearance tests show decreased values only when the condition is well advanced.

The renal lesion is progressive in proportion to the general rate of vascular deterioration. It frequently fails to reach the point of renal insufficiency because of death from vascular accident, coronary or cerebral.

Clinically there appear to be two definite clinical subgroups of this type, the benign and malignant. It is well known that some individuals tolerate a hypertension over long periods of time without much evidence of renal disease. In other cases a rapid renal degeneration is added to the hypertension and uremia results in a few months. Volhard and Fahr considered this to be due to the development of glomerular inflammation, and this would place the malignant type of Bright's disease as a combination of the hemorrhagic and vascular types. Certainly with the development of a clinically malignant hypertension there is an increase of urinary signs although not to the degree shown in the acute hemorrhage types. Retinitis is always present in the severe forms.

Case III.—A man, aged forty-four years, was first seen in the Clinic March 12, 1931. The patient's chief complaint was recurrent attacks of pain in the right ureteral area associated with urinary frequency and the passage of two urinary calculi



tient for urinary calculi. Renal degeneration was very rapid and had reached the stage of insufficiency and early uremia when death was caused by cerebral vascular accident.

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In children, the predominant type is the mixed tumor (Wilm's tumor) which usually occurs before the patient is ten years of age. Hypernephroma is the most prevalent tumor among adults, while carcinoma constitutes the second group of importance in the order of frequency. The perirenal myxomas, sarcomas, and a small group of miscellaneous tumors, are encountered much less frequently. Carcinoma and hypernephroma may occur relatively early in life. In this series the youngest patient with hypernephroma was thirty years old and the youngest patient with carcinoma was thirty-eight years old. Of the group with hypernephroma, 11 per cent of the patients were aged forty years or less while 63 per cent were aged fifty years or more. The average age was fifty-three for the patients with hypernephroma and fifty-six years for those with carcinoma. The average age of the children was five years. There seems to be a steady increase in the incidence of renal malignancies from the fortieth to the sixtieth years, after which time there is a steady decline in the frequency.

Hypernephroma and carcinoma occur more frequently in men. In this series of cases, 63 per cent of those with hypernephroma and 85 per cent of those having carcinoma were men.

Pain is probably the most frequent and constant symptom of a renal malignancy, but the pain is not especially characteristic nor is it always typical of a renal lesion. It may be dull, recurrent or paroxysmal. Severe renal colic frequently results from ureteral obstruction by blood clots or tumor tissue which cause an intermittent hematonephrosis or hydronephrosis and often simulates the pain associated with calculi. There may be only one or several mild attacks of pain over a period of years, and this may be the only symptom of a malignancy inoperable at the time of diagnosis. Many patients give a history of acute retention, the pain and retention being relieved by the passage of blood clots. When the pain is atypical, and is referred to the shoulders, chest, right upper abdomen, or associated with gastric symptoms, the clinical picture may be entirely misleading and disease of the gallbladder, stomach, duodenum, pancreas or appendix is often suspected. Every one is aware that

ROENTGENOGRAPHIC STUDIES IN THE DIAGNOSIS OF RENAL TUMORS

BERNARD H. NICHOLS AND E. LEE SHIFLETT

It is discouraging that cancer is so often hopelessly incurable before symptoms appear which can be definitely attributed to malignancy. In a large series of renal malignancies one is impressed with the frequency with which the primary lesion is first evidenced by large abdominal masses or extensive metastases. Many of these patients either have had no symptoms, or such obscure symptoms, that an early diagnosis of malignancy could not be established.

A review of a selected series of 100 proved cases of renal malignancy treated at the Cleveland Clinic presents some pertinent facts.

The controversy over the proper classification of kidney tumors makes published statistics as to the frequency of the various types of doubtful value and leads, in many cases, to confusion. In this series the tumors are classified according to the pathologic diagnosis recorded on the clinical histories at the time the gross and microscopic studies were made, regardless of subsequent clinical progress. The list is shown in the tabulation.

TABULATION

Hypernephroma.....	55
Carcinoma.....	5
Papillary carcinoma.....	9
Adenocarcinoma.....	3
Papillary Adenocarcinoma.....	3
Squamous cell carcinoma of pelvis.....	3
Tumors of childhood.....	16
Lipomyxosarcoma.....	3
Perirenal myxoma.....	2
Sarcoma.....	1

Malignant lesions of the kidney occur throughout the span of life but the greater percentage are noted during late adult life.

In general, the hematuria is shorter in duration, is more profuse, and occurs in a greater percentage of patients with carcinoma than with hypernephroma. Hematuria in our series had been present in 55 per cent of the cases of hypernephroma and was the presenting symptom in 40 per cent and painless in 29 per cent. Of the patients with carcinoma, 65 per cent gave a history of hematuria which was the presenting symptom in 48 per cent and was painless in 10 per cent. This greater severity of bleeding in carcinoma is partly indicated by the average of the hemoglobin determinations which was 74 per cent in cases of hypernephroma and 62 per cent in cases of carcinoma. A history of hematuria is not so frequently elicited in the mixed tumors of children. In the total series of cases of renal malignancy 52 per cent gave a history of hematuria.

Small amounts of microscopic blood in voided specimens is difficult to evaluate, but when present with other suggestive symptoms, it is further evidence of tumor. Microscopic blood in cystoscopic specimens, when considered alone, has no diagnostic value.

Frequency, nocturia, and burning on urination are prominent complaints. These symptoms often are caused by continuous irritation of the bladder by hemorrhage. Such disturbances may direct the attention to the bladder as the probable site of the disease while the underlying cause may be a renal malignancy.

A history of vague pains, or of indefinite gastric symptoms, all mild and unlocalized, may cause the patient to be considered a neurasthenic. Gastro-intestinal symptoms may dominate the picture, or may be the only symptom of a kidney tumor. In this series, four patients had as the presenting symptom some gastro-intestinal disturbance. These consisted chiefly of severe anorexia, nausea, vomiting, epigastric pain, flatulence and constipation, and occasional diarrhea. It was necessary to do a complete or partial gastro-intestinal roentgenographic study in 22 per cent of the cases of hypernephroma before a gastro-intestinal lesion could be excluded with certainty. Gastro-intestinal complaints were more frequent and

quite frequently, various abdominal operations are performed because symptoms from a renal lesion simulate those arising from a diseased condition of some abdominal organ. One often is not aided in the interpretation of this pain by the association of hematuria, and the presence of a palpable mass, the other so-called "cardinal symptoms" of kidney tumor which were found to be associated in only 25 per cent of the patients in this series.

The incidence of pain is greater and is more severe with carcinoma than with hypernephroma. Sixty per cent of the patients with hypernephroma complained of pain which was the presenting symptom in 17 per cent. Of the patients with carcinoma 74 per cent complained of pain which was the presenting symptom in 35 per cent. The pain is of relatively late onset in children but tends to become worse as the disease progresses.

Hematuria is a symptom both of benign and malignant renal disease, but in the presence of hematuria, malignancy should always be considered as a probable cause. Explanation of the cause or origin of hematuria by inference, based solely on the clinical history and the physical findings, should be done with considerable caution. The whole armamentarium of the clinician, surgeon, and the roentgenologist must be utilized, if necessary, to determine the cause of hematuria. A diagnosis of essential hematuria is never justified until every available means of diagnosis is exhausted in the search for other causes.

Hematuria may be continuous or recurrent over a period of years. In this series the average duration of this symptom was nineteen and a half months in cases of hypernephroma and thirteen months in carcinoma. There may be only one mild attack which disappears, and does not recur, and the patient and the physician are lulled into a false sense of security. Not infrequently patients give the history that urinary bleeding began after mild trauma such as twisting or straining, or after a prolonged period of stress or arduous work. The physician should never be content with this explanation of the etiology without further examination.

and the patient, a physician, attributed his state of health to infected tonsils. This case serves to illustrate the caution with which a conclusion should be drawn as to the origin and type of upper abdominal masses from the clinical history and the physical examination alone.



Fig. 200.—Urogram fifteen minutes after injection of intravenous dye. The right kidney shows poor function and a greatly deformed kidney pelvis. The detail is insufficient for definite diagnosis.

The roentgenogram of the kidneys, ureters, and bladder is an indispensable examination in all cases in which cystoscopy and pyelography are contemplated. If omitted, one is frequently unable to arrive at any conclusion from the pyelogram because of confusing shadows. This should always be the preliminary examination in cases of suspected renal malignancy. In the experience of the Clinic, this has proved to be of great value, not only in the investigation of renal tumors, but also

of greater severity in cases of hypernephroma than in carcinoma. In the latter, the chief gastro-intestinal symptoms was constipation, but occasionally there was diarrhea. Colby¹ states that gastric symptoms are more frequent with right kidney lesions than with left kidney lesions, because the right kidney by reason of its nerve supply is more intimately associated with the stomach, duodenum, small intestines and colon, while the left is more intimately associated with the descending colon and rectum. It is speculative that Colby's observation would explain the greater frequency of gastro-intestinal symptoms in the patients with hypernephroma, as 63 per cent of the hypernephromata involved the right kidney, while the smaller series of carcinomas were about evenly divided between the two sides.

The predominant physical finding in cases of renal tumor is a palpable abdominal mass. At the time when they first sought treatment, 78 per cent of the patients with hypernephroma and 50 per cent of those with carcinoma had palpable masses. Practically all the children had large abdominal masses when they were first observed by the surgeon. There may be other physical findings incident to a serious disease process, but these are not helpful in the specific diagnosis of a renal neoplasm.

It is often quite impossible by physical examination to determine whether or not an abdominal mass is present, and if present, to determine to what organ it is attached. Inference as to the origin will be correct in many cases, but it is often in error, and these errors occur frequently enough to justify an honest effort to demonstrate the origin and the type of enlargement by roentgenographic study or other special methods of diagnosis before final dispensation of the case is made. One patient in this series had a positive Wassermann and a right upper abdominal mass. It was thought that the mass was due to a syphilitic hepatitis. Months later, excretory urography revealed a malignant condition of the right kidney from which the patient died a few months later (Figs. 200, 201). This patient had no symptoms which would lead one to suspect a renal malignancy. His chief complaint was an unexplained fever

to the patient. The expense of this examination, when compared with the potential gravity of an abdominal mass, is negligible. In many instances it will seem unnecessary when the diagnosis is apparently self-evident from the clinical data, but it must be remembered that the "short-cuts" are the usual causes of errors resulting in grave consequence.

In this series of 100 cases, the probable site of disease, and in many instances a correct opinion as to the type of lesion was indicated in 75 per cent of the cases of hypernephromas, 30 per cent of the cases of carcinoma and in 50 per cent of the tumors of childhood by the stereoroentgenogram of the kidneys, ureter and bladder.

In the presence of a large perirenal tumor, when the subsequent pyelogram shows a normal kidney pelvis, the plane roentgenogram may make the diagnosis possible. The extent to which this examination is helpful in the direct diagnosis of a kidney tumor necessarily depends upon the various types of tumors, whether there is generalized cloudiness or localized enlargement, and the type of irregularity of the kidney shadow. It should be emphasized that a negative roentgenogram does not eliminate the possibility of a renal tumor. In suspected cases this examination must be followed by cystoscopy, pyelography, and intravenous urography when necessary.

A cystoscopic examination is required for a complete and thorough investigation as well as being a preliminary necessity to pyelography. There are no characteristic cystoscopic findings in a large number of renal tumors, and especially in cases of hypernephroma and perirenal tumors. The most frequent abnormality observed is a decreased or absent renal function on the involved side and a compensatory hypertrophy on the opposite side. In this series of cases of hypernephroma renal function was decreased in 42 per cent and absent in 8 per cent of the involved kidneys. Blood is frequently observed coming from the ureter of the affected kidney or in the bladder, either diffused with the urine or in clots. Transplants of carcinoma are frequently observed in the bladder or around the ureteral orifice. This abnormality was observed in 15 per cent of this

in the investigation of abdominal masses of all types. Confusing masses, from the clinical point of view, most frequently are Riedel's liver lobe, enlarged liver, ptosed or enlarged kidneys, fibromas, splenic enlargement, retroperitoneal masses and gastro-intestinal neoplasms. The origin of these masses can



Fig. 201.—The pyelogram of the right kidney illustrated in Fig. 200. There is marked compression and elongation of the kidney pelvis and calyces with moderate hydronephrosis. The better detail makes possible the diagnosis of hypernephroma.

not always be correctly determined by palpation. The stereoscopic examination of the kidneys, ureters and bladder often immediately establishes the nature of an abdominal mass, and in many instances eliminates the necessity of other roentgenographic study, and also indicates additional examinations in the proper direction without loss of time and additional expense

ciated with hematuria, papillomas, nonopaque stones, carbuncles of the kidney, and all types of benign cysts must be considered as possibilities in the differential diagnosis of tumor by pyelography.

The pyelogram may be entirely normal in the presence of large perirenal tumors. These are often confused with retroperitoneal tumors and at times the preoperative differential diagnosis can not be made. The plain roentgenograms often are of inestimable value in arriving at a correct conclusion in this type of tumor.

Pneumopyelography has not attained a great deal of popularity because of the fear of complications from air emboli. Those who have had considerable experience with this procedure are enthusiastic in recommending its use in the study of nonopaque stones, papilloma and hematuria with pelvic clot formation.²

In the Clinic series of cases of renal tumors, the pyelogram has proved to be the most valuable individual diagnostic procedure. It was possible to make a diagnosis of tumor, often specifying the type, in 64 per cent of the cases of hypernephroma and in 83 per cent of cases of carcinoma in which pyelography was employed. In most of the remaining cases, a serious pathologic condition of the kidneys was indicated but this could not be diagnosed as neoplastic from the roentgenologic evidence alone. When this was correlated with the clinical history, physical and cystoscopic findings, a preoperative diagnosis of renal malignancy was made in a very high proportion of cases.

Although the roentgenologist may not always be able to make a differential diagnosis between the various types of malignant tumors of the kidney, if he can determine whether a deformity is due to tumor, and decide between a benign and a malignant condition, he has rendered a great service to the surgeon.

Intravenous urography constitutes a great advance in the diagnosis of genito-urinary conditions, but it should not be substituted for retrograde pyelography in the study of renal tumors.

series of twenty-three cases of carcinoma. There is greater impairment of function, obstruction to the passage of the catheter more frequently, and more profuse hemorrhage, in cases of carcinoma. The cystoscopist is frequently able to make a diagnosis of probable renal carcinoma from these symptoms and findings. The diseased kidney was not functioning in 23 per cent of the cases of carcinoma. Cystoscopic examination is usually impossible in children but intravenous urography is an admirable substitute.

Whenever a carcinomatous growth is observed in the bladder near the ureter, especially if it be of the papillary type, the kidney should be eliminated as the primary site of the malignancy before operation on the bladder is undertaken.

It is impossible to present here a detailed description of the many variable deformities portrayed by the pyelogram in cases of renal tumors, and to discuss in detail the differential diagnosis. However, certain general principles which are helpful in arriving at a correct interpretation can be pointed out. The most frequent kidney tumors are the hypernephromas and the carcinomas. The hypernephroma originates in the kidney parenchyma, and as it expands within its capsule it displaces the pelvic structures and causes compression deformities rather than deformities by invasion, infiltration, or a filling of the pelvis. Often there is an associated enlargement of the kidney which corresponds with the location of the compression deformity. This type of lesion must be particularly differentiated from the various types of renal cysts. In carcinoma, the growth originates chiefly in the glandular elements or the pelvic structures and as it grows it invades and infiltrates the pelvis. There is more frequently no demonstrable enlargement of the kidney. Carcinoma must be differentiated from infections in many instances. When a hypernephroma is accompanied by hemorrhage there may be pelvic and ureteral blood clots which make it impossible at times to differentiate between these and carcinoma, papilloma, nonopaque pelvic stones and infections, particularly those infections associated with hematuria. Incomplete filling of the pelvis, duplex kidneys, infections asso-

Positive recognition or exclusion of renal malignancy from the clinical history alone is impossible because of the complex symptomatology. Pain, hematuria, and a palpable mass have been considered cardinal symptoms of a kidney tumor, but these were associated in only 25 per cent of the patients in our series. These are late symptoms and by the time they make a diagnosis unquestionable, operation has limited hope to offer.

Sincere cooperation between the various groups of the profession is absolutely necessary in making a diagnosis of renal tumor. The procedures leading to a thorough study should be employed in the following order: a careful history, a thorough physical examination, stereorentgenograms of the kidneys, ureters and bladder, cystoscopy, pyelography, and urography, when pyelography is inadvisable or impracticable.

The following case reports illustrate the difficulty of establishing a correct preoperative diagnosis of a renal tumor when clinical histories and physical findings fail to suggest the kidney as a cause of the patient's illness.

Case I.—The patient, a woman, aged forty-eight years, was first observed in 1923. She complained of dizziness, poor vision, frequent headaches and pain in the stomach which had been present for three years, and were gradually getting worse. There was no history of constipation, frequency, nocturia or hematuria. She had gained 10 pounds.

The physical examination revealed nothing of significance and the urine was normal except for an occasional pus cell. The blood count was normal. The blood urea was 21 mg., and the sugar was 135 mg. per cent. The phenolphthalein test showed that the total excretion in two hours was 55 per cent.

The diagnosis was obesity and probable chronic nephritis and hyperglycemia. The blood sugar was reduced to normal by dieting. In 1924, the patient returned, complaining of chills and fever and a generalized aching which had persisted for several days. The physical examination was negative except for a sense of resistance over the right kidney. The urine contained some albumin, 50 to 75 pus cells per high power field and a few organisms. The erythrocytes numbered 4,400,000 the leuko-

This method should be reserved for those cases of malignancy in which retrograde pyelography is impracticable, or impossible, as in children and a few adults on whom ureteral catheterization can not be performed satisfactorily. Intravenous urograms may be of great help in the diagnosis when metastasis to the ureter is present. Small tumors may not be shown, and even in the presence of large growths, a diagnosis may not be possible because of the lack of detail. This procedure determines the extent of damage to renal function, but one can not safely conclude as to the type of tumor present from function alone. It is not always possible to determine whether the neoplasm is an advanced or an early carcinoma. The function depends upon the amount of renal destruction and although carcinomas arising from the secretory elements of the kidney cause an earlier impairment of function than a hypernephroma originating in the parenchyma, an extensive hypernephroma by compression atrophy and fibrosis and rupture of the capsule with invasion may cause, in some instances, a greater decrease of function than an early or even advanced carcinoma.

Excretory urography has been used in a comparatively small proportion of our series of cases of renal neoplasm, but in practically all so studied, the presence of a tumor of the kidney was established. One should be guided by the type of deformity, as in the pyelogram, as well as by the function of the kidney in arriving at the diagnosis. Incidental cases in which the urogram shows a deformity suspicious of renal tumor should be checked by the retrograde pyelogram.

A critical review of the series of 100 cases of renal malignancy establishes many facts worthy of serious consideration. The extremely high mortality, the advanced stage of development, and the extensive metastases which are often the first evidence of a malignancy, impress one with the necessity of making an early diagnosis if the patient is to receive the greatest benefit from surgical or other treatment. There is no specific diagnostic aid and unfortunately no specific clinical symptoms in the early stage of the disease by which an early diagnosis can be definitely established.

conclusion from this examination was acute cystitis, compensatory hypertrophy of the right kidney and questionable tumor of the left kidney or ureteropelvic stricture, possibly from an aberrant blood vessel. The phenolphthalein test showed function of 30 per cent in the right kidney and only 1 per cent in the left. A pyelogram showed a deformity of the kidney interpreted as being due to a tumor of the left kidney.



Fig. 202.—The pyelogram of the left kidney shows almost complete elimination of the pelvis and calyces apparently due to a tumor of the kidney. At operation a papillary carcinoma was found. (Case I.)

A left nephrectomy was performed. The calyces were blunted and deep and the cortex averaged 8 mm. in thickness and was poorly differentiated in places. The pathologic diagnosis was papillary carcinoma of the kidney. This patient was last observed February 8, 1933. She had had no recurrence of papilloma and no bleeding, but had been under the care of a local physician for diabetes mellitus.

cytes, 10,800 and the hemoglobin was 85 per cent. The blood sugar was 114 mg. The clinical diagnosis was pyelitis, for which she was treated, but the symptoms persisted.

In 1925, she returned to the Clinic, still complaining. A glucose tolerance test was done and showed a diabetic curve. A roentgenogram of the colon was normal. A stereoroentgenogram of the kidneys, ureters and bladder was negative except for evidence of some arthritic changes of the spine. Cystoscopic examination showed that the urine was hazy and the bladder showed chronic inflammation. Catheters were passed easily to each renal pelvis and clear urine was obtained but there was slight retention on the right side. Catheterized urine showed 20 to 50 pus cells per high power field but no red blood cells. Urine from the right kidney contained a small trace of albumin and from the left was reddish in color and contained a large amount of blood and numerous pus cells. Both specimens were negative for organisms. Free fluid pus was pressed from the tonsils and the left ear showed a large scar from a healed perforation of the ear drum. Tonsillectomy and the removal of some infected teeth were advised to eradicate possible foci of infection.

Two months later the patient returned, complaining of pain in the back and in the head. She was still having some trouble with the left ear and throat. Symptomatic treatment was prescribed. The patient was not observed again for about fifteen months, but a follow-up letter stated that she had been having some fever during the latter part of 1925.

She returned again in October, 1926, complaining of considerable discharge from the right ear. This was treated symptomatically with relief. In November, attention was again directed to the kidneys because blood in small quantities, much pus and albumin were persistent findings in numerous voided specimens of urine. A cystoscopic examination showed cloudy urine and acute inflammation of the bladder. Catheters were passed to both kidney pelvises. There was rapid secretion from the right kidney but none from the left. There was compensatory hypertrophy of the right kidney. The left kidney could not be filled with pyelographic media (Fig. 202). The

The kidney tumor was discovered incident to the search for the origin of the abdominal mass.

Case III.—The patient, a woman aged fifty-two years, was first observed July 24, 1924. She had developed a persistent cough in the fall of 1923. The cough was productive and at times the sputum was blood-tinged, and on one occasion there



Fig. 203.—Roentgenogram of chest showing metastasis from hypernephroma. (Case III.)

had been a rather severe pulmonary hemorrhage. She had had pleurisy-like pain in the chest for approximately eight months. She also had night-sweats. Seven months before admission, persistent pain had developed in the right hand and the right shoulder. The appetite was poor. There was no history of frequency, dysuria, nocturia or hematuria. She stated that

Case II.—A man, aged fifty-five years, was first observed October 30, 1923, complaining of a tumor in the abdomen. He said that he had had liver trouble for five years, and for the last five weeks had had considerable gas formation, was becoming increasingly constipated and was suffering considerably from nausea. The appetite had been fair but he had lost much weight and his strength was failing. Certain foods were distressing and he had had to eliminate meat from the diet. There were no genito-urinary symptoms. Several roentgenographic examinations of the gastro-intestinal tract had been made, with negative findings.

The only significant finding in the physical examination was an irregular, movable, nontender mass in the right iliac fossa. The diagnosis from the clinical and physical findings was carcinoma of the ascending colon.

A catheterized urine specimen showed a slight trace of albumin, glycosuria, 15 to 20 red blood corpuscles per high power field, and an occasional pus cell. No casts or organisms could be demonstrated. The hemoglobin was 75 per cent. The roentgenographic examination of the colon showed no evidence of disease. Cystoscopic examination showed clear urine and a mild trigonitis. Catheters passed to each renal pelvis and there was no retention in either kidney. The pyelogram showed that the kidney pelvis was rotated and tubular in shape but the deformity was not typical for tumor. The preoperative diagnosis was right hydronephrosis and possible malignancy.

Right nephrectomy was done on November 9, 1923. When the kidney was exposed, there immediately appeared a large mass, involving the right kidney. The mass measured 14 by 10 cm. in size, and in one area invaded the kidney tissue for a distance of several centimeters and at one point extended into the kidney pelvis. The microscopic examination showed hypernephroma. The patient died June 1, 1925.

This case is one of a huge tumor of the kidney, the symptoms of which were gastro-intestinal. Several x-ray examinations of the gastro-intestinal tract had been entirely negative.

casional red blood cell, 1 to 6 pus cells per high power field, and a few granular casts.

A roentgenogram of the chest showed metastatic malignancy of both lungs and of the right ribs posteriorly (Fig. 203). There was a destructive lesion at the upper end of the radius not involving the head and two areas of destruction in the skull (Figs.



Fig. 205.—Radiogram showing several areas of destruction in the skull caused by metastases from a hypernephroma of the kidney. (Case III.)

204, 205). These were regarded as metastatic lesions from a primary malignancy. No operation was advised because of the extensive metastases.

The patient died in January, 1925. The autopsy showed that the left kidney was very lobulated and the kidney parenchyma had been destroyed. The renal vein was greatly dilated and filled with tumor tissue which proved to be an extensive

she had had a lump in the left side for eleven years and this had gradually increased in size. The patient had had an operation for the removal of a nodule on her skull which she said was dead bone.

The patient was emaciated, her pulse rate was 100 and the blood pressure 120 systolic, 80 diastolic. There was a fluctuant mass over the anterior frontal region of the skull. Percussion and auscultation revealed no abnormalities in the chest. The

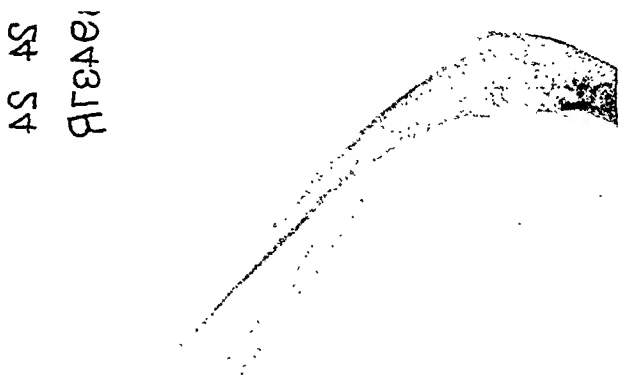


Fig. 204.—Roentgenogram showing destruction of the upper third of the right radius by metastases from a hypernephroma of the kidney. (Case III.)

thyroid was moderately enlarged. There was a large, hard, movable mass in the left flank. The right kidney was palpable. The clinical impression was metastatic carcinoma from a primary growth of the bronchus or thyroid.

The blood count showed 3,970,000 red blood cells, 7000 white blood cells and 75 per cent hemoglobin. The Wassermann reaction was negative. The voided specimen of urine showed no sugar or Bence-Jones protein but contained an oc-

casional red blood cell, 1 to 6 pus cells per high power field, and a few granular casts.

A roentgenogram of the chest showed metastatic malignancy of both lungs and of the right ribs posteriorly (Fig. 203). There was a destructive lesion at the upper end of the radius not involving the head and two areas of destruction in the skull (Figs.

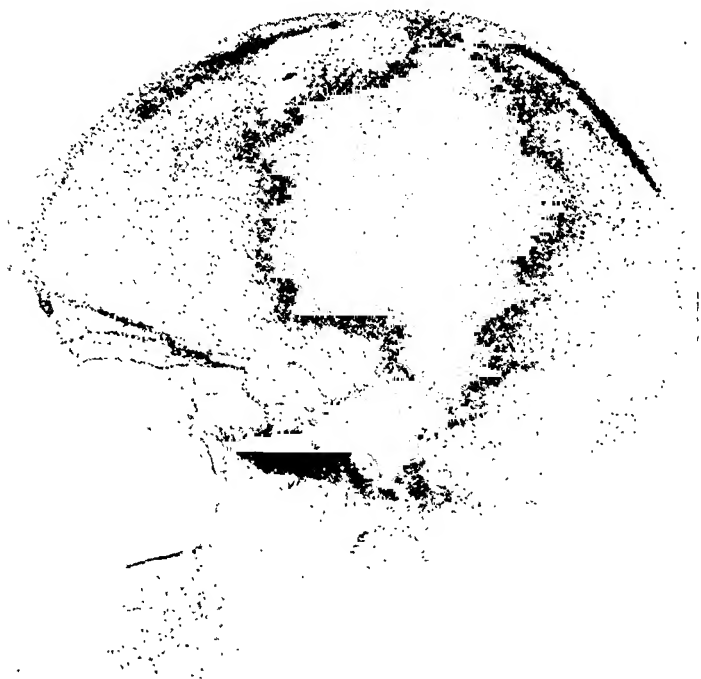


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The patient died in January, 1925. The autopsy showed that the left kidney was very lobulated and the kidney parenchyma had been destroyed. The renal vein was greatly dilated and filled with tumor tissue which proved to be an extensive

hypernephroma of the left kidney. Sections of the skull and arm showed the destructive areas to be metastatic lesions from the hypernephroma.

In this case, the symptoms were caused by extensive metastases to the skull, chest, clavicle, forearm and ribs. Although a mass had been present in the left side for eleven years, she had never had genito-urinary symptoms. The clinical history was that of a primary malignancy of the lung. The roentgenographic findings of metastatic lesions were confirmed by autopsy which disclosed a hypernephroma of the kidney as the original neoplasm.

Case IV.—A woman, aged sixty-four years, was first observed May 9, 1926, when she complained of loss of weight and strength which had begun nine months earlier and had progressed until she had lost 56 pounds. Two months before admission she had begun to have soreness in the left lumbar region and this had become gradually more severe and finally extended across the lower abdomen. She had been constipated for two or three months. Her only urinary disturbance was nocturia once each night which had been present for years. There were no gastric disturbances. She had become more nervous during the past few years. She was emaciated and cachectic. The mucous membranes were pale. The lungs and heart were normal. There was a firm, apparently fixed and tender mass about the size of a grape fruit in the left upper abdominal quadrant.

The clinical impression from the history and the physical findings was carcinoma of the colon or an enlarged spleen.

The urine showed a faint tract of albumin, red blood cells and 2 to 10 pus cells per high power field. The blood count was 4,180,000 red cells, 6700 white blood cells and 65 per cent hemoglobin. The urea in the blood was 30 mg. and the Wassermann reaction was negative.

Roentgenographic examination of the colon was normal. On cystoscopic examination, the ureteral catheter passed a little slowly to the left renal pelvis and there was 10 to 15 cc. of retained urine on this side. A differential functional test

glandlike structures lined by flattened and cuboidal epithelial cells that were vesicular and pale-staining. There were numerous papillomatous growths into large spaces and solid masses of tumor cells. The tumor cells were large, with considerable cytoplasm, somewhat vacuolated. The nuclei were rounded or oval, vesicular with fine, granular chromatin. In some areas the epithelial cells were arranged in long, tubelike structures, suggesting tubules of the kidney. Ureteral structures were not identified. The pathologic diagnosis was adenocarcinoma of the right kidney. The patient died April 27, 1929.

Case VI.—A woman, aged thirty years, was first observed on November 1, 1932. She said that for six or eight years she had suffered from discomfort and soreness in the right side which was worse at the time of the menses. Dieting and diathermy had afforded some relief until a pregnancy caused the discomfort to return. One year previously she had discovered a mass in the right upper abdominal quadrant. This was tender and painful especially during the menses. She had some urgency, frequency, and burning micturition, and these symptoms also were exaggerated during menstruation. Nine months previous to admission, she had been jaundiced. She had lost 4 pounds in weight.

The physical examination was negative except for a large mass, quite firm, not tender, in the right upper abdominal quadrant which was separate from the liver edge and moved freely with respiration. The clinical impression from the history and physical findings was hypernephroma of the right kidney.

The urine contained blood and a slight trace of albumin, and the blood count showed 5,380,000 erythrocytes and 5800 leukocytes. The hemoglobin was 94 per cent; the urea 30 mg. The Wassermann and Kahn reactions were negative. The cystoscopic examination was normal. The pyelogram showed a very large right kidney with hydronephrosis of the upper portion of the pelvis (Fig. 206). The lower portion of the kidney was greatly enlarged.

Right nephrectomy showed the kidney to be five times

feces. The blood count showed 30,700 white blood cells, urea in the blood was 24 mg. and the Wassermann reaction was negative. The gastro-intestinal x-ray examination showed an extrinsic lesion, probably of the liver or pancreas. The stomach, duodenum and intestines were normal. A roentgenogram of the chest was normal except that the right diaphragm was elevated. The stereoroentgenogram of the kidneys, ureter and bladder showed a mass in the right upper abdominal quadrant.

The cystoscopic examination showed that the bladder was atonic and very sensitive, the trigone was congested, the posterior bladder wall was finely trabeculated. The right ureteral orifice could not be catheterized. Sacral anesthesia was administered and 5 cc. of indigo carmine was given intravenously. The secretion from the left ureteral orifice was copious. No dye could be seen in the right ureteral area nor could a right ureteral orifice be found. The cystoscopic diagnosis was old pyonephrosis and perinephritis.

Exploration of the abdomen revealed numerous adhesions and high up behind the liver a large extraperitoneal mass was palpated. A fluctuant mass was exposed which approximated the size of a large cantaloupe. When aspirated, a brownish, odorless material was secured which contained shiny crystals resembling cholestrin. The total amount of this material was 500 cc. The cyst had a very definite wall and at one point, normally corresponding to the kidney pelvis, there were numerous large blood vessels. The removal of the cyst left a space extending high up under the diaphragm. Exploration failed to reveal a definite ureter but along the course where a ureter would normally lie there were numerous hard nodules. The operative diagnosis was retroperitoneal cyst.

The large cystic mass, measuring 14 by 12 by 8 cm., contained many cholesterol crystals. The wall varied from 1 to 10 mm. in thickness. A small layer of tumor tissue was found in the cyst. Microscopic examination showed that there were a few scattered remnants of glands or tubules, probably representing remnants of the original kidney tissue. The capsule of the tumor persisted. The tumor tissue consisted of irregular,

normal size. It contained no cysts. The microscopic diagnosis was hypernephroma of the lower pole of the right kidney.



Fig. 206.—Pyelogram showing a large hypernephroma of the lower pole of the right kidney. The pelvis is displaced upward and there is a hydronephrosis of the upper pole. (Case VI.)

The patient was well when last observed on December 20, 1932.

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pustules on the surfaces of the nodules and some areas were crusted. The hairs in the lesions could be removed with the slightest traction. The upper lip, which was covered with a mustache, was not affected. Hairs removed from the lesions contained many large spores and mycelia in and about their roots.

The patient was admitted to the hospital and a course of nonspecific protein therapy was administered intravenously in the form of typhoid vaccine. Potassium permanganate packs

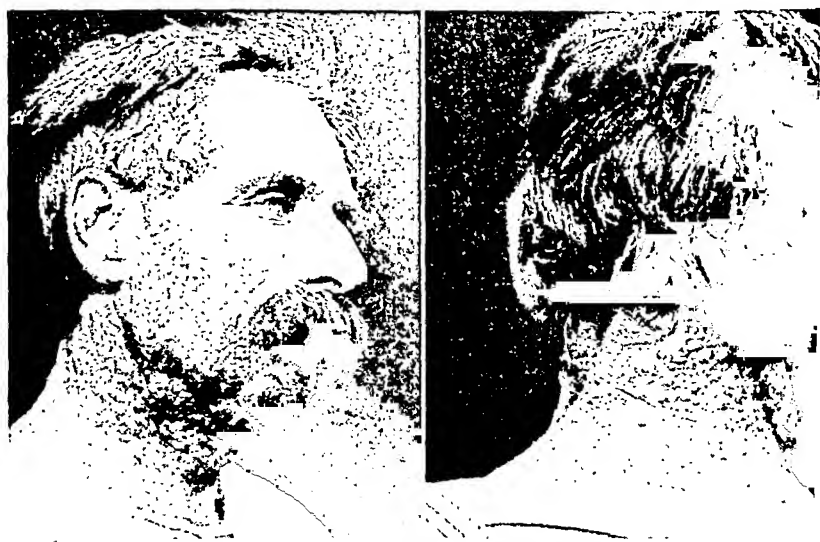


Fig. 207.—Case I at time of admission.

followed by dressings of ammoniated mercury ointment were used to remove the crusts and to prevent contamination of other areas. The patient's temperature on admission to the hospital was 99 degrees. Six intravenous injections of typhoid vaccine were given, one every other day. The first ampoule of a prophylactic set was used. The initial dose was 66,000,000 organisms and the largest dose 160,000,000. Following the second and third injections there was a severe chill. The highest temperature was 103 degrees. Subsequent injections did not produce such severe reactions.

TINEA SYCOSIS. WITH SPECIAL REFERENCE TO TREATMENT WITH INTRAVENOUS INJECTIONS OF TYPHOID VACCINE

EARL W. NETHERTON

RINGWORM infection in its various manifestations comprises a large proportion of the cases seen in the average dermatologic practice. The anatomic and physical peculiarities of the regions involved as well as the type of causative fungus alters the clinical manifestation of ringworm infection. This is well demonstrated in tinea sycosis, a comparatively rare type of ringworm infection, as the clinical picture of the nodular type differs greatly from that seen in the more common types of fungus infection. It is the most disfiguring and repulsive lesion caused by fungi and usually responds slowly to treatment.

In 1926 Engman¹ reported on the value of foreign protein therapy, which he had found beneficial in cases of large spored ringworm infection of the beard in adults and of the scalp of children. His contribution has not received the attention it deserves from authors and clinicians. The purpose of this report is to record our experience with this treatment in the nodular type of tinea sycosis.

Case I.—A farmer, aged forty-seven years, came to the Clinic February 23, 1925, complaining of an eruption on the face and neck. His past and family history was irrelevant. The fact that a few of his cows had a scaly eruption was elicited, but he had not considered this of any importance. The patient's skin eruption had been present for six weeks, having started as a red, scaly area on the right side of his neck. Soon thereafter numerous pustular lesions appeared on the face and neck. He had used various topical applications without relief.

The eruption was limited to the hairy portions of the face and neck (Fig. 207). It consisted of large, dull red, boggy nodules and small follicular papulopustules. There were small

corner of the mouth, limited to the bearded area, there was an oval, well-defined, raised, soft, nodular, bright red granulomatous lesion about two inches in its longest dimension. The surface had a glossy appearance. Crusting had been prevented by the use of an ointment. There were a few small pustules on the surface. There had been some loss of hair in the area involved. The remaining hairs could be removed with the slightest traction (Fig. 209).

Microscopic examination revealed many spores and a few mycelia within and about the hairs which had been removed

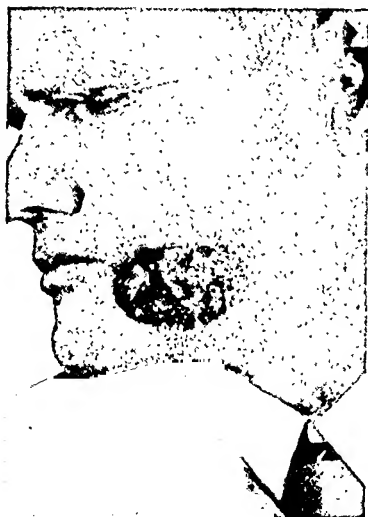


Fig. 209.—Case II prior to treatment with typhoid vaccine.

from the lesion. Hairs were fixed in formalin and paraffin sections were made. These showed clusters of round bodies thought to be spores, but no mycelia were observed. Cultures on Sabouraud media did not grow a fungus. The Wassermann and Kahn reactions and other laboratory tests were negative.

When the patient was admitted to the hospital his temperature was 98.2 degrees. Five injections of typhoid vaccine were administered intravenously, one on alternate days, and the last dose was 500,000,000 organisms. The highest temperature

After four injections there was marked improvement in the skin condition. The size of the nodules was decreased and the smaller lesions were disappearing. At the end of two weeks he was discharged from the hospital greatly improved, but a few small lesions remained on the neck and so a subintensive roentgen irradiation was applied to these resistant areas. When



Fig. 208.—Case I six weeks following treatment.

he was seen six weeks later, the skin eruption had disappeared entirely (Fig. 208).

Case II.—A farmer, aged forty-one years, came to the Clinic on January 30, 1933, because of a "sore" on the face. His past and family history had no relation to his complaint. Ten weeks prior to admission he had noticed a red spot on the lower portion of the left side of the face. The lesion had gradually enlarged but had remained superficial and scaly for five weeks. It then became crusted, raised, tender and increased in size rapidly. There had been no systemic symptoms except that he had noticed that he was listless and fatigued easily.

A general examination revealed nothing abnormal besides the lesion on the face. On the left side of the face near the



Fig. 211.—Case III showing nodular lesions of tinca sycosis.



Fig. 212.—Case III. Note nodular lesions on posterior surface of neck.

produced by these injections was 103.2 and the patient had slight chills. After the third reaction the lesion was less tender and began to decrease in size. The loose hairs were removed and a dressing of ammoniated mercury ointment was applied.

He was discharged from the hospital on the eleventh day and advised to continue the use of the mercury salve. The lesion was about one third its original size. When seen six



Fig. 210.—Case II six weeks following treatment.

weeks later the lesion had disappeared, but there was some scarring (Fig. 210).

Case III.—A farmer, aged fifty-eight years, was referred to the Clinic, because of an eruption of the face and neck. This was accompanied by itching, a slight amount of soreness and rapid enlargement of the lesion. He thought he might have a carbuncle. A week after the appearance of the first lesion similar papules began to appear on the bearded portion of the face and neck.

On the left side of the chin and the right posterior and anterior surfaces of the neck there were raised, dark red, deeply seated, nodules and infiltrated areas. Their surfaces were

He was a well-developed and well-nourished young man. On the right side of the chin and bearded portion of the face there were four light red, raised, soft, granulomatous nodules, whose (Fig. 213) surfaces were studded with small follicular pustules and crusts. Most of the hairs in the infected areas had been removed, but, a few loose, broken off hairs were present in some of the lesions. The lymph glands of the right side of the neck were slightly enlarged and tender. Hairs removed from the nodules contained spores and mycelia, and a positive culture of trichophyton was obtained.

The patient refused to go into the hospital for treatment. All visible hairs were removed from the lesions with tweezers and potassium permanganate packs and dressings with ammoniated mercury ointment were applied. One-half a skin unit of unfiltered roentgen irradiation was given. He was seen again on January 29, 1933, at which time he was almost well. Another one-fourth skin unit of unfiltered radiation was applied to the diseased areas. He did not return for further observation.

Case V.—A policeman, aged thirty-one years, was seen on October 8, 1928, because of a lesion on the upper lip which had been present for several days and was enlarging. He had previously been treated at the Clinic for psoriasis, which had cleared up almost completely.

There was a dark-red, raised, well-defined, flat, crusted lesion about 1.2 centimeters in diameter on the left side of the upper lip. The crust was loosely adherent. When the crust was removed several small follicular pustules were observed. The few remaining hairs were easily extracted with tweezers (Fig. 214). The regional lymph glands were not enlarged or tender. The patient had never grown a mustache. Many spores and a few mycelia were found within and about some of the hairs. The Wassermann and Kahn reactions were negative.

All hairs were removed from the surface of the lesion. One-half a skin unit of unfiltered roentgen rays was administered every two weeks, for three treatments, and potassium iodide was given by mouth. On December 29, 1928, the lesion had completely disappeared.

studded with small follicular pustules. The hairs in these areas could be extracted easily. There was no acute painful cellulitis around the lesions and no systemic symptoms were present. The upper lip which was covered with a mustache was free of lesions (Figs. 211, 212). Hairs from the lesion contained many large spores and mycelia. The diagnosis was tinea sycosis and he returned to the referring doctor for treatment.

Case IV.—A farmer, aged twenty-four years, came to the Clinic on July 14, 1931, for treatment of an eruption on the



Fig. 213.—Case IV. Presenting only a few lesions.

face and neck which had persisted for five weeks. The lesion had started as an itchy "pimple" on the chin, and had developed into a superficial, round, scaly spot which he thought was a ringworm. In a short time this area became thickened and crusted and new spots developed on the face and neck. Ultra-violet light therapy was followed by rapid enlargement of some of the lesions.

bility of syphilis was excluded by the negative reactions of the Wassermann and Kahn tests.

All visible hairs were removed with tweezers, and moist packs of a saturated solution of sodium hyposulphite followed with applications of sulphur salve were advised. Within three weeks the lesion had practically disappeared. He returned to the Clinic on January 19, 1925, because of a recurrence of the infection at the site of the previous lesion. Three-fourths



Fig. 215.—Case VI. The associated regional lymphadenitis makes this case of special interest. Such findings are suggestive of primary syphilis.

of a skin unit of roentgen radiation filtered with 1 mm. of aluminum was given and the patient was also advised to take potassium iodide. He did not return but a letter received from him two weeks later stated that the nodule was about one-third as large as it had been at the time of our last observation.

DISCUSSION

There are two types of tinea sycosis: (1) the superficial or dry type, and (2) the nodular or suppurative type. The



Fig. 214.—An example of a solitary lesion on the upper lip.

This case is of interest because of the rarity of involvement of the upper lip in this disease.

Case VI.—A farmer, aged twenty-four years, came to the Clinic on November 25, 1924, complaining of a sore on the left side of the chin (Fig. 215). Twenty days before our first observation he had developed a small pimple on the left side of the chin. This had gradually enlarged until it was about 2 centimeters in diameter. Two weeks later he had noticed some enlargement and tenderness of the submaxillary lymph glands. There were no constitutional symptoms.

On the left side of the chin there was a round, raised, dark-red, soft, granulomatous nodule, with a few small follicular pustules on its surface, which were most numerous at the margin of the lesion. There were only a few hairs on the central portion of the nodule. Near the periphery, the hairs were loose and could be removed easily, and these contained many spores. The submaxillary glands were enlarged and tender. The possi-

ing sycosis vulgaris, to large, raised, boggy, cutano-subcutaneous nodules of a carbuncular type. The nodules are dull to bright red, soft and their surfaces are crusted or studded with follicular pustules. At times the surface of the lesion may be glossy. The crusting is the result of the matting of exudate and beard rather than ulceration. The suppuration is produced by the fungus and not by a secondary invasion of a pyogenic organism. Seldom do large abscesses form. Usually many of the hairs in the nodules have fallen out and those remaining can be removed easily with tweezers.

Contrary to what might be expected from the appearance of the patient, the eruption is not accompanied by troublesome subjective symptoms. The early lesion may itch slightly and the more advanced suppurative lesion may be slightly tender or painful. The regional lymph glands are sometimes enlarged and tender. Williams² is of the opinion that in such cases the lymph glands have become infected with the fungus. Some recent observations tend to support this opinion. White⁴ was able to demonstrate by culture and by direct smear the presence of trichophyton interdigitale in material obtained from an enlarged inguinal lymph gland. The same fungus was obtained from the interdigital space which was drained by this gland. Sutter⁵ obtained a positive culture of trichophyton granulosum from a kerion, a softened regional retro-auricular node and an associated trichophytid.

Constitutional symptoms usually are absent; however, in exceptional cases there may be general malaise, chilling and a slight rise in temperature. It is probable that patients with lymphadenitis have a slight fever more often than is suspected. I regret that the temperature was not determined in every case in this series.

Occasionally a generalized eruption, usually of the lichenoid type may develop in cases of tinea sycosis. This is analogous to the trichophytid that sometimes occurs in kerion in children. Those who are especially interested in the phenomenon should read Williams' excellent article.

Etiology.—Tinea sycosis is the result of an infection by

nodular form may start as a superficial scaly process or the superficial type may develop suppurative lesions; however, since the fungus found in the respective types usually differ, a mixed type of this disease does not occur.

The superficial type is rare in Cleveland. It starts as one or more small red areas which soon become scaly and enlarge peripherally. As the lesions enlarge, they may become confluent, forming irregular, festooned plaques. The central portion of the lesion may be less inflammatory as in ringworm of the glabrous surfaces of the body. The hairs in the infected area break off and at times their stumps appear as black dots on the surface of the lesion or there may be some hyperkeratosis at the follicular orifices. The hair either comes out spontaneously or can be removed with the slightest traction. The inflammatory reaction usually remains superficial, but it may extend deep enough to produce some infiltration of the lesion, and in rare instances, there may develop some follicular suppuration. This type is similar to the microsporon infection of the scalp in children.

The suppurative or nodular form is the most common type of ringworm infection of the beard. The chin, the bearded portion of the neck and the lower portions of the face are the areas most frequently involved. Strangely, the upper lip is rarely affected, even in cases with extensive involvement of the other portions of the bearded area. Williams² states that *tinea barbae* involving the upper lip is a medical curiosity. Davidson and Dowding³ have suggested that the mustache which was so popular in the past protected the upper lip from infection and intimated that the present fashion of shaving may be accountable for more instances of the disease on the upper lip. There is no apparent reason why this region should possess a special immunity to this infection.

The initial lesion may be of the superficial type just described or an inflammatory papule. There may be one or multiple lesions and the rapidity of spreading of the eruption and the severity of the inflammatory reaction varies. The lesions vary from a small, follicular, red papulopustule, simulat-

dry type of ringworm infection of the beard from impetigo. Some of the nodular lesions of tinea sycosis may superficially resemble a carbuncle or furuncle. The latter conditions are more painful and accompanied by acute cellulitis and constitutional symptoms. An annular tubercular syphilid with its dull red infiltrated margins can hardly be confused with the superficial type of tinea barbae, especially if scarring and pigmentation have resulted. Eczema or dermatitis venenata is seldom limited to the bearded region, it is usually poorly defined, involves the interfollicular areas and is accompanied by intense itching.

Regardless of one's clinical experience or diagnostic acumen the diagnosis must be confirmed by demonstrating the fungus in the hairs. Several loose hairs should be removed from the lesions and placed on a glass slide in two or three drops of 20 per cent solution of sodium hydroxide and covered with a cover glass. In one hour the preparation should be examined under the microscope. As the hairs dissolve, spores and mycelia may be seen in and about the intrafollicular portion of the infected hairs. It may be necessary to examine several hairs before the fungus is found. Hairs should be planted on slants of Sabouraud's media, but, as a diagnostic procedure, this is inferior to direct examination, for cultures frequently remain negative in cases in which the fungus has been demonstrated microscopically in the hydroxide preparation.

Treatment.—As previously stated, tinea sycosis does not respond readily to treatment. However, the common parasitocidal remedies used in the treatment of other varieties of ringworm infection produce a cure if used persistently. As in ringworm infection of the scalp, it is essential that all of the infected hairs be removed. If there are only a few lesions, the hairs may be removed with tweezers, but of course, this is not feasible in extensive lesions, and some authorities recommend epilating doses of roentgen irradiation. Dressings moistened with saturated solutions of sodium hyposulphite followed by sulphur ointment or lotions of bichloride of mercury followed

the large-spored trichophyta of the ecto-endothrix type. They are generally of animal origin, consequently farmers, grooms, veterinarians and others who frequently come in contact with domestic animals are the ones most often infected. This type of fungus usually produces marked inflammatory reaction with suppuration. The endothrix is found within the hair shaft while the ectothrix remains about the hair but penetrates it to some extent. The ectothrix type produces the most suppuration. It is desirable to have detailed information concerning the causative fungus, but such knowledge does not materially influence the method of treatment. Only the experienced mycologist can properly determine what fungus is present. Cultural studies are necessary for the proper classification of fungi. However, the less experienced can, as a rule, distinguish the large and small spored type of ringworm by a microscopic study of the infected hair. It should be remembered that it is only the large-spored ringworm infection that is benefited by foreign protein shock.

Diagnosis.—Tinea sycosis is most likely to be confused with sycosis vulgaris, lupoid sycosis, impetigo, contagiosa, carbuncle and furunculosis. Eczema, seborrhoeic dermatitis, annular tubercular syphilid and other eruptions commonly seen on the face can be differentiated by careful and accurate study of the lesions.

Sycosis vulgaris is observed most frequently on the upper lip, as a chronic nasal discharge often is an etiologic factor. Suppuration is moderate, and the pustules are small, follicular and usually pierced by a hair. The hairs of the infected follicles do not come out spontaneously nor lift out so readily as in tinea sycosis. Pustules continue to appear, usually in a few hours after all infected hairs have been removed. It is not uncommon for several pustules to develop overnight. There may be some infiltration in chronic areas but deeply seated nodules do not occur.

The chronicity and cicatricial alopecia distinguish the chronic suppurative folliculitis of lupoid sycosis. The absence of follicular involvement and broken off hairs differentiates the

in the rapid response to treatment, as the second patient responded equally well without any irradiation.

The nodular type of tinea sycosis is analogous in many respects to kerion. It differs, however, in that with the development of suppuration there is not a spontaneous disappearance of the lesion. The explanation of this difference in these otherwise similar conditions is not known.

Foreign protein shock treatment is the most satisfactory type for nodular tinea sycosis, for a cure is obtained more quickly than with other types of treatment. It is probable that the increased cellular resistance which is produced by non-specific protein shock is a factor in hastening the involution of the nodules.

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with white precipitate or calomel ointment are valuable topical applications. The beard should be kept short.

Foreign protein shock is a valuable adjunct in the treatment of this recalcitrant disease. Engman was the first to report on its value. With McGarry,⁶ he treated two patients with large-spored ringworm infection of the beard with a vaccine which had been prepared by Strickler from cultures of microsporon from the scalp. Strickler⁷ had obtained favorable results with this vaccine in ringworm infection of the scalp in children. Engman and McGarry's results were better than those obtained from other forms of treatment. Because of the favorable results with this nonspecific vaccine, and since benefit had resulted from the use of foreign protein in the form of typhoid vaccine in the treatment of other dermatoses, Engman decided to use typhoid vaccine in the treatment of tinea sycosis. Five patients with the suppurative type of megalosporon infection, two of the beard, and three of the scalp were treated. A cure was obtained sooner than by the usual methods.

Typhoid vaccine* was employed in the treatment of the first and second patients in this series. The eruption in the first case was so extensive that no effort was made to remove the hairs. Antiseptic dressing was applied as a precautionary measure. In the second case, the hairs were removed daily as the lesion subsided. The suppurative lesions disappeared equally well in both cases. A complete and more rapid cure was obtained in these two cases than in Cases IV, V, and VI, where the ordinary methods were used. Although roentgen rays were used in Case I it is doubtful whether this was a factor

*The vaccine used for the protein therapy is prepared by adding 1 cc. of stock typhoid vaccine to 9 cc. of sterile normal sodium chloride solution. One cc. of this suspension contains 100 million organisms. The initial dose is $\frac{1}{4}$ cc. Subsequent doses are double that of the preceding injection. If a reaction is not obtained the dose is increased. Injections should be given every other day and five or six reactions should be produced. Improvement is usually noticed after the third or fourth injection. Since most of the patients with tinea sycosis are young, healthy persons, there is seldom any contraindication to this form of therapy. However, it should not be employed on patients with cardiorenal damage, tuberculosis and other debilitating conditions.

No longer does the profession feel that the diagnosis of cardiac disease is part of a death sentence, and our patient, the layman, has been also taught to look on the general classification with less horror and more optimism—perhaps with more resignation because of the things which we may do for him and because of the courage which we may rightfully instill into him. I am not a cardiologist, but an internist and I wish to speak to you from this point of view in particular, the cure of the patient who has a cardiac defect and not of the specific care of any disease in particular.

My first patient has been loaned to us by Dr. Gill Richards. I had the pleasure of seeing this young lady in his office yesterday and she has been so very courteous as to come before us for she represents a very interesting condition and as Dr. Richards and I told her yesterday, one which justifies optimism for her future.

Case I.—I shall give but the essential points of her history. Miss M. B. is twenty-three years of age. She comes of a fine, vigorous family of pioneer stock. There are no taints of tuberculosis, of cardiovascular disease, of endocrine defect or the like in her history. Her girlhood was essentially negative except for the various trivial infections to which most children fall. About twelve years ago she had an attack of sore throat which was not believed to be of serious nature and from which she made an early recovery in so far as the acute symptoms are concerned. She was attended by an excellent physician at the time. We do not know whether or not a throat culture was taken, but shortly after this she developed some paralysis of the throat and her attendant then stated that it must have been a diphtheria in spite of its apparent mildness. She was kept in bed until the paralysis had completely recovered and longer because she had also developed a cardiac arrhythmia; "trouble with the heart," the precise nature of which we can only surmise, probably it was the typical effect which this grave infection so commonly caused in the days before antitoxin.

From this time on she continued with her ordinary school work. She was clever and attractive, and took part in the usual school activities apparently without hindrance. While never athletic, she was still able to dance, walk, play the usual games and so on without any hindrance, "she was not sick." She has always been sensitive and nervous, high strung.

Two years ago she was in an automobile accident in which she was not injured materially, but it upset her a great deal nervously and since then she has remained very emotional, sensitive; at times very introspective. School life ceased to be attractive and she was very unhappy. She tired easily and experienced frequent attacks of vertigo. Following this accident she was exam-

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CLINIC OF DR. HARLOW BROOKS

BELLEVUE HOSPITAL

THREE CARDIAC CASES¹

It is a very great pleasure for me to again appear before you. I believe that I had the honor of appearing as your first speaker when these Clinics were inaugurated several years ago, and I have always felt extremely grateful to you for the fact that you have continued to ask me to come. Your tolerance is certainly high, for I have had the pleasure of speaking before you since that first period on many other occasions and on each you have sent me back home feeling more and more that I have become a sort of adopted son of Utah and of this beautiful city where I have so many valued friends and where I am always so very happy and content.

You have selected for me today three cardiac cases; I shall try to present them in the light which modern medicine has now made possible in cardiac disease, that is, in a light of optimism, for although we are as yet entirely unable to cure many cardiac conditions we have certainly learned very well how to make many of its victims not only comparatively comfortable, but also reasonably efficient, and though we may not cure many diseases of this character, no more than we cure the often closely allied disease of birthdays, still life and comfort which we are now able to continue for long periods of time are, after all, all that we can accomplish in any condition, cardiac or otherwise.

¹ Given before the Clinics of the Utah State Medical Society, Salt Lake City, Utah, September 14, 1933.

even though she is admittedly very nervous before this very dignified, but, as she says, good-looking group of men. You observe that she has a sense of humor. Her basal metabolic rate has been determined previously during a quiet time. It is well within normal variations. Her tonsils are well out; her teeth, buccal cavity, tongue and upper respiratory passages are all in good condition. As I show you her knee jerks are exceedingly active, all her normal reflexes are in similar state. Mentally she is very intelligent, she has some sense of humor, but she is too introspective and she has melancholy periods which make her very unhappy, for has she not "heart disease" and therefore is she not likely to pass out at any time? Is it not true that her life must be greatly circumscribed, that she may not marry or conduct the ordinary domestic responsibilities appropriate for a young lady of twenty-three years?

It is perfectly true that she has heart block, and in all probability it originated from her attack of diphtheria of twelve years ago. The picture in my mind of her pathology is that there is a patch of fibrous tissue which has been laid down somewhere in the bundle of His, a fibrous replacement of degenerated fibers such as our good friend, Dr. Aldred Warthin, told you here a few years ago takes place in diphtheria. I picture an old healed scar which causes a break in the conductivity of the bundle, hence her heart block. This lesion is certainly not progressive, for there is no hypertrophy of the heart and no malformation under the fluoroscope. We believe that the valves are intact and in so far as we can surmise the muscle reserve of her heart is not far subnormal, if in the least so. Aside from her arrhythmia, and there is no doubt about that, she is free from all evidences of cardiac disease and she has had this arrhythmia since her attack of diphtheria twelve years ago.

There is something however about the young lady herself that we must point out and we must treat that, for I do not think that her heart itself requires any medication. Since her automobile accident and her discovery that she has heart disease, she has lived in terror and unhappiness, she has cut herself off from her friends and her amusements, from her work at the University. She cannot see herself as you and I see her, a very attractive young woman, of intelligence and charm, but only as a cardiac derelict. I dissent from her diagnosis on all points and so does Dr. Richards. I would diagnose the young lady herself as a pretty healthy young woman who has been unnecessarily frightened by the discovery of a heart lesion which is giving her no trouble and which may never do so, unless she is very foolish and attempts things which she should not do.

We have advised her to go back to the University, to take

ined physically at the University, and was advised not to do any strenuous exercise because she had some irregularity of the heart.

She was first examined at the Salt Lake Clinic in November, 1932, at which time she showed a complete auricular-ventricular heart block. The auricular rate at this time was 95 per minute and the ventricular rate was 64. (Please recall that this young lady is highly nervous, as you see for yourselves today.) Yesterday when I saw her with Dr. Richards she had a ventricular rate of but 38. The general physical examination was essentially negative. I shall not take the time to go into the details of the record. The heart measured on the 7-foot plate, median right, 3.5 cm.; median left, 9 cm. As I hold up her plate beside her you will note that this is a small or certainly not more than a normal sized heart for a girl of her build, for she is of good size and general proportions. Her cardiac rhythm today is very irregular. The ventricle drops about every third beat. There is a slight soft systolic murmur at the apex, it does not seem to be organic. She has never suffered from any rheumatic or septic-like disease. A2 and P2 are practically normal. Her thyroid is slightly enlarged, but it is uniform and soft in texture. Her blood pressure is 124/80. The urine is negative. The blood shows a slight anemia of a secondary type in spite of her fine color as she appears before us today.

During the past year she has continued to have some attacks of vertigo and she gets very weak. She has become very apprehensive about her heart and she has become exceedingly despondent for has she not "heart disease"? Aside from the knowledge that she has this condition, she has little to complain of. She is able to walk, to dance on occasion, she is not short of breath, her digestion is good, she is never cyanosed, there has never been any edema of the ankles. I probably should have told you that the electrocardiogram shows the typical picture of a two to one block. Here it is. One does not however need the electrocardiogram here to make the diagnosis of block, for in spite of her embarrassment and nervousness it is a very easy matter to make out and count the rapid jugular pulse and to compare it with the much slower ventricular rate counted at the apex.

There are no râles, no moisture at the lung bases. The liver is not enlarged, neither is the spleen. She is not in the least cyanosed, in fact she shows no evidence of cardiac defect except the arrhythmia. Her chief complaint is the knowledge that she has "cardiac disease." Her story of vertigo is somewhat unconvincing. Neither Dr. Richards nor I have seen her while she was suffering in this respect, but of course the thought occurs that these attacks may represent a Stokes-Adams syndrome. I am not inclined to assume this, until we have further evidence for there are other facts which bear directly on this complaint of vertigo.

I have already mentioned the fact that she has a prominent thyroid gland, this you all see for yourselves. It is notably prominent today, more so than yesterday, but there is a physiologic reason for this today, for when she is menstruating the gland usually enlarges somewhat as it does in many young women of her highly organized type. She has no subjective tachycardia today, her apex rate just now is 42, the jugular pulse is much more rapid but I cannot count it. Her hands are cold and sweating, but there is no tremor,

quent, after he had attained old age, though he refused to retire, and he died in his office at over seventy years of age, suddenly and from a large coronary thrombosis, which had been probably antedated during the battle of Gettysburg, by an initial coronary attack, for in the region of the bundle of His we found at autopsy an old calcified scar as though from an old but small cardiac infarction. But he had lived for fifty years thereafter a useful and intense life, in which very few limitations of any manner had been practiced.

Of course I know that stories of this character are a matter of no surprise to all the doctors here, but I thought it might reassure our young patient to feel that she too may have to work hard and pay taxes for fifty or more years.

(The patient leaves the room and another case is wheeled in on a hospital bed.)

DR. BROOKS: Of course gentlemen you all realize that I have attempted to make our clinic of therapeutic value to our patient for I believe that fright and introspection are doing her more harm than her heart block.

Case II.—This patient entered the hospital about fourteen days ago. She is over seventy-six years old. She has raised a good-sized family, has always worked hard and continued to do so up to about one month ago, when she was obliged to give up her regular work, and to allow others to help her. She came to this state a long time ago, of course not one of the very early pioneers, for note she is but seventy-six or so years old now, but she married a rancher in her youth, and has lived the hard and exacting life of a ranch wife and mother since. She gives an almost negative past history. She does not recall the usual diseases of childhood, but she probably had them, for she was one of a fairly large family. She has never had typhoid fever, pneumonia, rheumatic fever or any other grave infection. She has had no incidents requiring surgical treatment, but has, she thinks, suffered from the usual traumatic and sick incidents, such as pass without particular note in women of her character. She has borne without difficulty several healthy children, now all adults. Her menopause was without incident.

This brings us to the present history, for I may say that this woman has passed through what has probably been a very hard life, without comment or complaint, accepting the hardships of the settler with the philosophy characteristic of her kind.

About two or three months ago she noted that she was losing strength, that she could not do her work, or walk upstairs with her accustomed speed and energy. She was not losing weight, but on the contrary her abdomen was notably swollen at night and her ankles were swollen also, so that the

part in the social events there, to do her work, to be very certain that she receives plenty of sleep, plenty of good, iron-rich food, for in spite of her rosy Salt Lake City color, she has a tendency toward anemia. Surely she should not go in for athletics but I see no reason why she should not dance and walk. She should not go out into your high hills on mountain climbing trips, but she will be benefited by going to the usual student picnics and by having generally a good normal lady-like student's life. Further I do advise her when the discerning young men up at the University look in her direction that she do not turn her face away and cultivate the marble heart, I believe that is what the young boys in school call it, but that she consider herself as a reasonably well and very fortunate young lady.

Partly for our patient's admonition and partly for yours, I wish to tell you of the first instances of heart block and of Stokes-Adams syndrome that I ever recognized.

At the Battle of Gettysburg there was an enthusiastic young second lieutenant standing in line awaiting the order to counter charge. He suddenly lost his consciousness and fell to the ground. He thought, and his comrades thought that he had fainted from fright or from the excitement incident to the action. He soon aroused and was able to take part in the battle but ever afterward he was subject to attacks of sudden fainting which in such instances was always accompanied by a sudden very slow heart rate. This was the very first case of heart block and of the Stokes-Adams syndrome that I had ever seen. Of course I did not meet him until over fifty years after the battle of Gettysburg. Our young second lieutenant had by this time become a much respected judge, but he had always throughout his legal career been handicapped by the fact that under great excitement or of anger, and he was a decidedly peppery type of man, he would go into typical heart block with the Stokes-Adams syndrome. He lived over until the invention of the electrocardiograph and his was the first instance in which I saw in the cardiogram, a true heart block. The attacks became more and more fre-

how flabby the general muscles are and she does look her birthdays. She has a splendid spirit and feels that she is able to return to her own home and to her usual responsibilities, but we shall not agree with her in this last respect, for although we are willing to discharge her now we are entirely unwilling that she should be allowed to return to the heavy work and undue exercise to which her former duties submitted her.

The pulse is now quite regular and the volume of the first or muscle tone of the heart is good, it is not clear however and there is a certain fuzziness and muffling which spells a defective heart muscle, though no actual murmur is to be made out. The valve closures are not accentuated and the blood pressure is 160/90, quite a satisfactory finding when age, previous history and all are taken into consideration. The urine is of course of low specific gravity, it contains a few hyaline casts, a mere occasional trace of albumin; it is the urine in brief of a chronic interstitial kidney, or the kidney of old age. The blood chemistry shows also a slight retention of nitrogen beyond the normal, or the usual, which is perhaps the better term to employ. The blood uric acid is 4 mg. per 100 cc., the creatinine 3.2, the urea nitrogen 20 mg., the blood sugar is but 78 mg. per 100 cc.

I note that there is a marked generalized arteriosclerosis evident in the retinal vessels which show also a good deal of calcification. How may we appraise the pathology in this patient from what we have found and from what we know of her history? How may we direct her life and her medical management so that she may enjoy a maximum of comfort and health for a maximum length of time?

In my opinion it is most helpful from a therapeutic standpoint to attempt to picture in your own mind, the pathologic processes at work in your patient and to proceed from this standpoint to that of what may be done to afford the best result for your patient in terms, first of comfort, and next in duration of life. From our history, from the findings of the gentlemen of the staff at her admission and from her present condition which is as we all must appreciate a beautiful illustration of what may be done for cases of this kind. We must assume that the primary fault on her admission was a slowly increasing cardiac failure. In all probability this but moderately enlarged heart presents no valve disease beyond perhaps a certain degree of relative dilatation of the mitral and aortic rings but the muscle is the most important thing to be considered. The picture in my mind is that of a dilated heart of moderate degree, the muscle is rather light brown in color, a brown atrophy of the muscle. The coronary vessels are like the *radials*, the *temporals* and the retinal vessels, they are sclerosed and calcified. Because of this my assumption of a brown atrophy of the muscle is probably reasonably correct.

The lungs of course show the usual associated conditions, a certain degree of emphysema which is compatible with her years and the somewhat barrel shape of the chest. The kidneys, I picture as small and hard with adherent capsules, with sclerotic arteries—they are the kidneys also of old age and the parenchyma has suffered from the laying down of surplus connective tissue between the tubes and in the glomeruli. I mention the *shrunk*en, arteriosclerotic kidney normal to old age, premature or natural.

feet and ankles showed shoe and stocking marks on their removal. She had become markedly short of breath, and had developed a good deal of cough, apparently without other symptoms of a cold. She was no longer able to lie flat in bed on her back with comfort, and found her breathing more easy when she was bolstered up on many pillows. She also found that she could often sleep with more comfort seated in a comfortable chair rather than by going to bed. Her most insistent complaint has, however, been because of "indigestion." Food disagrees with her, she has much gas, some of which she is able to eructate. She has lost her appetite and there is abdominal discomfort even if she eats very little or nothing, in fact it does not seem to be the character of the food taken that is at fault, but only that food is taken at all.

Physical examination has shown a very commonplace but important picture. She showed on admission quite marked cyanosis especially of the lips, of the hands and feet. There was marked edema of the pendant portion of the body, the abdomen was prominent, the hollow viscera were distended with gas and the liver was readily palpable through the edematous abdominal wall, 7 to 10 cm. below the costal margin. The spleen also was readily palpated and both liver and spleen were tender. Some ascites was undoubtedly present. The breasts were edematous and even in spite of the edema the peripheral arteries, the brachials and radials, the temporals and the femorals, popliteals and the tibials were markedly sclerosed and probably calcified.

There was some shifting fluid in both pleural spaces, a good many moist and sibilant râles were present over the entire lung area and the patient insists that she had real asthma at times. The heart was found markedly large, the pulse and apex beats were irregular; there was a considerable pulse defect. Dyspnea was marked and so also was cyanosis. She was suffering severely from orthopnea, unable to speak, to eat or to sleep. The urine output was very small.

The diagnosis of cardiac failure as a result of myocardial degeneration was made. This was probably primarily due to arteriosclerosis and the changes incident to old age.

Wisely instead of waiting for the effects of digitalis the young gentleman of the House Staff promptly gave her a sufficient hypodermic of morphine with the result of giving her immediate relief and that most important universal panacea of all, sleep. This was followed by the adequate and speedy administration of digitalis by the rapid method. As a result of this prompt and correctly designed treatment within three days our patient was in comfort. Within a week she was able to sit up, to lie down without discomfort and her progress has since been rapid so that now she is able to get up and about, under her own power, as it were. She can walk around the ward and is so comfortable that her chief complaint now is that she has been retained here in the hospital.

As you see, she is no longer cyanosed, there is no edema present. She breathes easily and there is no cough. The liver has receded to the costal border, the spleen is no longer palpable, the abdominal wall is flabby. It shows, however, the markings of its previous edema and no doubt if she were allowed to become too active there would be a general ptosis for you note

crease the routine amount of digitalis, one may give on the so-called "rest days" a combination of digitalis, of a good laxative and a diuretic. Such a preparation has been known for many years as the Fothergill or St. Bartholomew's pill, or in Germany as the Niemeyer's pill. Each pill contains equal parts of calomel, squills and digitalis leaf. They may be made up 1 grain of each constituent, and given once, twice or three times daily so that one or more days weekly is given for the relief of my surplus fluid which may be retained in the tissues.

The best diet for these cases must be also determined, as it were, experimentally. Where the patients are thin and malnourished it will as a rule be found that the patient will do well on any diet representing adequately most of the normal food elements in balanced proportion. Even where the vascular tension is somewhat higher than we might like to see, if there are no evidences of very definite abnormal retention in the blood chemistry it is usually well to let the patient select his own foods from those which he knows that he can tolerate with comfort and pleasure.

Even where the heart has once decompensated as in the case in question when compensation has again been effected, it is usually better to encourage mild exercise for the heart muscle like all other muscle will deteriorate but the faster when it is given no exercise, but of course the patient must be cautioned not to overdo especially in this respect.

In conclusion, the skilled practitioner has found that by such simple measures as we have discussed today we are usually able to keep our old age decompensated case in reasonable comfort often for a long time by the proper use of rest, food, sedatives, very temperate exercise and almost always by the prolonged routine use of digitalis.

So we shall send this lady back to her family doctor with instructions to the effect that she must keep in touch with him, and she must continue to keep up the few drugs which have done so much for her here. She must be reasonably careful about her diet, and if she does these simple things, not by any

Now, what can be done to give this woman all the comfort and the normal expectation of life for one of her age and condition? Therapeutic pessimists may say very little, of course we cannot give her a new heart or a new kidney, but when we recall the condition in which she entered the hospital and that in which we now see her, we are furnished an illustration of what may be done by an intelligent physician and a co-operative patient. From suffering and discomfort she has been restored to comfort and content.

Few, except the skilled family practitioner, realize how much may be done for these old persons. Rest is of course the keynote. Our house physician promptly gave our patient a dose of morphine, and wisely. He followed this up by the prompt and adequate administration of digitalis and the present condition of the patient is the direct result of this treatment. It is obvious that we no longer require morphine but the bromides, chloral and many of the newer similar drugs may be used to continue as may be needed sedation so that our patient gets sufficient rest, relaxation and sleep. This is beyond doubt one of the very numerous cases of old age in which the systematic giving of digitalis will work wonders for the comfort of the patient, perhaps for an indefinite length of time.

One must not attempt to maintain these cases on large doses of digitalis, but rather to find by experiment the dose and that form of the drug which will maintain the circulation at its optimum. In this case I imagine that 1 or 2 grains of a good powdered leaf given once daily may entirely suffice. If it does not, it may be increased until the proper amount is determined. I like, if possible, to reserve however one or two days weekly on which no digitalis is given, and on these days with old people I like to give calomel, magnesium sulphate or some other diuretic and laxative so that the excessive amounts of fluid are entirely removed from the body tissues and the satisfactory excretion of any surplus digitalis which may have been stored up may be also accomplished. Where there has been no enlargement of the liver, and it is not desired to in-

The laboratory studies of the patient are in general negative. The Wassermann test is negative, the blood picture is entirely normal in so far as morphology is concerned, and the blood chemistry shows no striking changes, sufficient to indicate renal or hepatic disease. The urine is, however, of rather low specific gravity, 1.006, the amount of urea and of the chlorides is low. No casts are present. There are a few leukocytes in the sediment, a few epithelial cells but it is otherwise negative. Her basal metabolic rate has been determined, just why I do not know, but anyway it has been found to be well within the normal limits.

Physical examination, however, shows the wisdom of her home physician's advice. The pulse is somewhat rapid, 100 per minute. It has a feel of fulness. The systolic stroke is forceful, it shows an occasional drop beat and counted at the apex it is found that this represents a somewhat futile systole of the left ventricle. There are no cardiac murmurs but the valve closures, especially at the base, are very sharp and ringing, almost metallic. Of course we are taking account of the fact that our patient just at present is somewhat excited and perturbed, but these sounds are more suggestive than one would expect naturally under such circumstances alone.

Though she is quite well nourished, it is not difficult to percuss out the outlines of the heart. The right border appears to be about 6 cm. from the median line and the left border shows a point of maximum apex excursion well outside the nipple line and quite 10 cm. or more from the midline. This heart is certainly enlarged and auscultation shows it to be definitely over-acting. The arrhythmia is shown by the electrocardiograph to be of the sinus variety; this record shows otherwise a quite normal mechanism, but the degree of left ventricle preponderance is certainly more marked than should be. I am sure that her own physician did not require this aid to properly estimate this patient's status, but it is very helpful to us to know that the cardiac mechanism is about normal, for, clearly, we are dealing with heart difficulty in this case in spite of the patient's lack of striking circulatory symptoms. Any student after having listened to this heart should at once suspect serious changes in blood pressure and the reading taken a few moments ago shows 210/120. These figures are altogether too high to be caused by some intercurrent and transitory emotional state. They mean disease.

Our patient is too plump to permit of satisfactory palpation of the brachial, popliteal or tibial arteries, the temporal arteries do not especially attract the attention. The radial vessels are of small size, but notably cordlike and hard. The ophthalmoscope, however, tells us the story in a most convincing way. The retinal arteries are small, they reflect the light in the characteristic way spoken of as "silver wire," they are contorted for the arteries of so young a woman. The veins of the retinae are congested and contrast sharply with the small wirelike arteriols and as the veins pass over the arteries, a definite compression of the venous caliber is evident. There are no true degenerative lesions present, but in the right retina at about two o'clock is seen a small recent hemorrhage. The picture alone is that of an early phase of an essential hypertension. Probably the retinal picture in this condition is one of the most characteristic phases of it.

The negative blood chemistry and the practically negative urine findings

means forgetting that she has as a handicap the matter of a few birthdays and a great deal of hard work back of her, she may get on in comfort and with pleasure to those about her for a long time.

(Patient leaves the room and Case III enters and seats herself.)

Case III.—Our last patient today is this vigorous, energetic woman of thirty-five years. Her chief complaints are few. Because of a trivial incidental sickness her physician gave her a general examination and as a result of this he told her that she was sick and that she required attention.

This lady is but thirty-five years of age. She is married and has three healthy children. Her marital history is otherwise negative. She has had no grave infection. She denies a knowledge of typhoid, pneumonia, of tuberculosis and the like. There is no surgical history. Her recollection of the diseases of childhood is very vague. Family history is however of some bearing. Her father died from an apparent cerebral hemorrhage at the age of about fifty years. An older brother also suffers from high blood pressure, though he is but forty years of age.

The patient reported to her physician recently because of increasing headaches which had been appearing with greater and greater frequency and severity and apparently without cause. After an examination he pronounced that her heart was seriously diseased, that she had high blood pressure and that she required a considerable modification in her customs of life, and regular supervision.

There is very little in her general appearance to suggest the need of these precautions. She is very well nourished, is red-checked, energetic, she is rather overweight, perhaps, but there is nothing in her pounds to suggest disease origin and she tells me that she resembles in the main her father's type of physique; they were all well-nourished, energetic people. There is no cyanosis, but after exercise there is a slightly suspicious bluish tinge to her full red lips. She has no edema. She is, perhaps, slightly dyspneic and she has noted that on going about her house of late that she has had to slow down somewhat in her customary gait as she goes upstairs because of shortness of breath.

Her bowels are open and regular but she does have to get up once or twice at night to void a full bladder of urine. She is sensibly fond of her food but does not overeat, and she generally prefers the simple but well prepared articles of ordinary diet. She does not smoke but she occasionally takes wine or beer and an occasional cocktail, though she is not in the least dependent upon these for comfort.

She is evidently an emotional woman but is usually good natured and always self-controlled. Note that the eyes are a bit prominent, she has a short, rather full neck, and her thyroid gland is evident, but not strikingly so. She has had her babies rather closely together. The hands are normally warm, the capillary return is good and rapid, she shows no edema of the ankles. She has as a whole the appearance of a healthy, intelligent, energetic and well-balanced woman.

The dangers in cases of this kind lie in one of three directions. Either her chief danger lies in the danger of rupture of a blood vessel, usually in the brain, in the production of a thrombosis or embolism from a dilated or otherwise diseased heart, or from giving way of the heart itself. In this particular instance the greater danger seems to lie in the heart for most of the few symptoms and signs now manifest lie in and about the heart. She is somewhat dyspneic, has noted some physical inadequacy and she shows a considerably dilated heart while the vascular changes elsewhere, notably in the retinal vessels, are in a rather early stage of the disease. She probably is in infinitely more danger of a dilation of the heart than from a cerebral hemorrhage or embolism, though her developing symptoms of headaches are significant in this direction.

It behooves us then to particularly conserve the heart in our management of the case. In this direction, I feel that our first care is to see at all times that there is no unnecessary physical activities. She must not hurry, especially in the performance of physical work of any kind whatever. She must not walk up stairs unnecessarily and when she is obliged to do so she must be slow in the accomplishment of her act. She should not walk against the wind, nor should she undertake games, particularly competitive ones which assume physical effort. Since golf is so widely a sport now perhaps we may illustrate her restrictions in relation to it. I should interdict the game as such, unless she will be content with a very flat and not too difficult course and that she expend her greatest time in simple putting, she must not attempt to outdrive her friends, nor should she ever forget that even on the most level of courses that it is but a game and if she experience any difficulty or discomfort that she is to stop at that instant and not attempt to carry on to keep up the foursome, etc. The fact is that a certain amount of exercise is necessary for the best welfare of the heart, she should walk on the level some daily, except when otherwise ill or when she is feeling badly.

Emotional stresses of all kinds must be also avoided in so

are highly confirmatory of the diagnosis of an essential type of hypertension in contradistinction to one dependent on a primary renal defect and again the lack of a historical background for a renal hypertension is highly suggestive of this diagnosis.

The patient as yet shows practically very few or no striking signs of the disease and symptoms are also largely wanting. This tends to indicate its probable type as from an hereditary tendency, suggested also by her meager family history and since her physical type is like that of her paternal relative, who died from a similar disease, this probability seems all the more likely. Evidently from the considerable size of the heart the condition has been of some time standing, for the heart shows a degree of hypertrophy which must have taken years for its development which therefore was slow in origin. For all these reasons I think that we are justified in the diagnosis of a mild or innocent type of essential hypertension rather than one of the malignant type or form.

I certainly feel that our patient has been correctly advised to put herself under care and observation at this time when symptoms are so largely absent, rather than to wait until the decrease has become so advanced that it is readily recognized by the patient and repaired or conserved with so great difficulty by the physician.

Obviously our patient who is indeed almost a picture of health and who is herself little aware of her illness is not a hospital case, nor need she feel that her days are numbered. Of course we all realize with an increased blood pressure of this degree there is danger of vascular rupture, of embolism or of thrombosis, but, at the same time we know that the average case of this kind in intelligent persons who cooperate with their physicians and other well wishers usually go on for a long time of useful and oftentimes highly productive lives before their condition has become such as to demand intensive care.

Very much has been written about weight and overweight in hypertension. It is of course, obvious that the more weight carried, the more effort must be expended to do this and therefore it is desirable to hold weight down, perhaps to reduce it moderately, but certainly not to the extent of starving of the essential organs of the body or of unbalancing her metabolic needs by an unbalanced diet. One must also in this relation recall her family type. Do what we may, she is certain to follow this unless we alter the tendency with measures so strict as to probably seriously compromise her welfare. This matter of weight then must be, as it were, worked out experimentally and that weight will be found most to her advantage at which her capability and her nervous and mental reactions as well, are at their best. We shall not change her ancestral type.

sedative effects of tobacco are so manifest that it is wise to continue its use in a temperate manner.

As to the use of medicines. There are very many of us who feel that when the heart begins in this condition to manifest evidence of its inadequacy, as by the development of hypertrophy, certainly when the conductive system shows evidences of failure, digitalis should be used in small, so-called "tonic" doses. To illustrate this point in this particular instance, today I should be inclined to give this patient small doses of digitalis, perhaps a grain or so of the powdered leaf daily until such time that I had relieved her slight dyspnea. There is nothing which so induces dilatation as dilatation and it is wise to scotch it before it has become established as a habit.

When early signs of distress appear, I should resort early to the experimental use of the nitrites, if they obliterate the symptom, good, let it be kept up, but if not, of course, it should be discontinued.

The sedatives are often of tremendous value particularly in highly emotional or excitable persons. The bromides are still my favorite often with chloral as my drug of second choice, but the various combinations of barbituric acid are also very useful in those instances in which they appear to act best.

The question has been asked, how about further pregnancies in such a case as this? I should be unalterably opposed to this and where the question constantly arises some of the various methods of contraception should be practiced.

Now as to prognosis. I feel very certain that by good medical care in such an instance as this, one may tremendously conserve life, duration, comfort and pleasure in life while it lasts. I feel quite certain that if this young woman will see her family practitioner at more or less regular intervals, say once monthly when she feels perfectly well and more frequently when things are not going so well, she will be richly repaid in the comfort and pleasure that she will get out of life and in the duration of it.

Just a word in closing. The public has been so widely

far as possible and she should now on especially attempt to cultivate self-control and placidity not only of action but also of thought.

She must never overload the stomach, especially when she is to walk or otherwise exercise. She must be sure that she gets adequate rest and it is a very good practice to take a daily afternoon nap or rest, especially when her life demands that she be out that evening. It is all a great mistake to cut these patients off from all varieties of diversion and pleasure—I am quite certain that such a procedure really shortens life, it certainly renders it not worth the whole. Eight or more hours of nightly rest must be insisted upon. She must content herself to limit however her unnecessary responsibilities, under whatever guise they may be classed, service on committees, etc.

A little as to habits, first as to tea and coffee. If she is able to sleep satisfactorily when these stimulants are used temperately, there is no objection toward their employment unless perhaps in some definite way as from the production of an indigestion they may cause some trouble. As a matter of fact the drug effect of tea and coffee is to dilate the coronary vessels, to stimulate the cardiac muscle and to increase its irritability, in fact these drinks are good for all those cases in which we would be inclined to give the salts of caffeine or theosin. The phobia against the normal use of these pleasing drinks has been, perhaps, largely inadvertently due to the advertising efforts of commercial interests whose function is to substitute therefor an entirely inert and mostly worthless substitute.

To some extent the same may be said as regards to the temperate and legitimate use of alcohol. There is no longer any doubt as to the beneficial effects of alcohol in the prevention of arteriosclerosis and in the cases which suffer from this condition it may be beneficially employed always and only in most temperate and never intoxicating amounts.

Tobacco is almost always harmful, I believe, though I enjoy it very much myself, but there are cases in which the

lightened as to the matter of heart disease that it is a good plan to have a tremendous benefit which will come to our care even though we do not as yet replace a heart valve. It prevents decompensation of the heart but half a chance and our work of the years has amply justified a test of the patient, under modern conditions of treatment.

I thank you for the attention you have manifested in my clinic. You further evidence to justify the many cases of heart disease.

tension, malignancy, erythemia and infectious metabolism may arise, many skin diseases in diabetes.

A patient receives little from basal metabolism. It is characteristic of the disease is usually 30 per cent. A basal metabolic rate of a total lack of 10 per cent has been found in the administration of the diet can be successfully exercised. In following the basal metabolic rate do not. An unmarried patient of myxedema. The patient is within normal. Subsequent to the daily of the symptoms of basal metabolic rate of the patient when the daily intake of the patient is broken symptoms and a rapid

those met in the clinical questionably improved sufficient to the normal range. They are

BASAL METABOLISM

The level of the basal metabolism is now recognized by both physiologists and clinicians as one of the best indications of the activity of the thyroid gland. As early as 1893 Friedrich Müller called attention to the emaciation and loss of weight in spite of the high caloric intake in exophthalmic goiter patients which suggested to him that the total metabolism was increased in this disease. By 1897 Magnus-Levy had demonstrated an increased oxygen consumption in hyperthyroidism, and diminished oxygen consumption in cretinism and myxedema. It was not until 1912 that the work at the Russell Sage Institute of Pathology and Carnegie Nutrition Laboratory provided us with an apparatus and method for the determination of basal metabolism which was suitable for clinical purposes. Since then the apparatus has been simplified and improved so that at the present time basal metabolism determinations have become a part of the routine in all well-organized clinics and many doctors' offices. As a test of thyroid activity basal metabolism determinations have proved of great value in diagnosis and treatment of the diseases of the thyroid gland. There are, however, certain limitations of a laboratory test of this type. The technic while not particularly difficult is full of pitfalls which may lead to errors amounting to 10 or even 20 per cent. The normal standards in general use are for most purposes adequate but it should be remembered that an occasional normal individual may have a basal metabolism well outside the range set as normal for the test. The diet and state of nutrition are important. In the undernourished the metabolism is lower while in the well nourished it may be elevated. The state of mind, the trained *versus* the untrained subject, and muscular tone are all factors necessary of consideration in slight or moderate variations from the normal mean. While there may be a tendency of errors in different directions to neutralize one another there is always a possibility of a combination tending to a large discrepancy in a single instance. In certain diseases there are well-recognized variations from normal. A slightly elevated

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METABOLISM IN HYPERTHYROIDISM AND HYPOTHYROIDISM¹

A COMPREHENSIVE review of the field of metabolism in diseases of the thyroid gland is obviously an impossible task in the brief space at our disposal, nor would it serve the purpose for which these gatherings are designed. During the past two decades the interest of the physiologists and physicians in the subject has resulted in numerous investigations which have brought forth now well-established facts of great value to the practitioner. The purpose of this talk is to consider some of the practical problems in the diagnosis and management of diseases of the thyroid in so far as alterations in metabolism are concerned.

By far the most common diseases of the thyroid are believed to be due to either diminished or increased activity of the gland, in its elaboration and discharge into the general circulation of the hormone thyroglobulin. Of the thyroid insufficiencies, myxedema in adults and cretinism in children are easily recognized clinically. The diffuse symmetrical enlargement of the thyroid gland at puberty and in the low iodine areas are associated with a slight insufficiency. All conditions in which there is overactivity are usually designated as hyperthyroidism, "toxic thyroids" or exophthalmic goiter. Fortunately malignant disease of the thyroid is much less common as is also acute and chronic thyroiditis.

¹ Read at the Graduate Fortnight of the New York Academy of Medicine, October 23, 1933.

suffering from disturbances other than within the thyroid gland. The administration of thyroid gland as a therapeutic test is probably the best method of differentiating these cases. In addition to this effect on the clinical condition the basal metabolic rate control is of great advantage. Thyroid gland should be given in amounts sufficient to bring the basal metabolic rate to within normal limits. Occasionally the result is spectacular and improvement is striking. In other cases without any change in the basal metabolic rate the patient may complain of accentuation of existing symptoms and no clinical benefit result. Still others with large doses of thyroid extract no beneficial change is observed in the clinical picture nor is there the expected rise in basal metabolic rate. Carefully controlled administration of thyroxin by mouth or parenterally may be tried. The low basal metabolic rate in our experience is encountered most frequently among those patients who complain of nervousness, easy fatigability, sensitivity to cold and menstrual disorders. They are usually individuals who are worried over their ability to maintain a satisfactory social or economic position in the community; lack force of character, have a low blood pressure; and are poor physical specimens. As a rule their basal metabolic rate is seldom lower than -20 per cent and it is in this group that thyroid gland therapy is most disappointing. A small percentage of patients apparently exhibit what seems to be a true hypothyroidism, the basal metabolic rate is usually as low as -25 per cent or lower and they improve with thyroid gland administration.

The adolescent goiter is associated probably with slight insufficiency. Frequently the girls have a basal metabolic rate between -15 and -20 per cent. The normal variation of the basal metabolic rate among youths of the adolescent age is greater than among adults, frequently on the low side. Most of the individuals with adolescent goiter living outside the endemic goiter areas probably need little treatment. It is our practice, however, following the advice of Marine, to administer small doses of thyroid substance (Burroughs Wellcome

metabolism is frequently found in hypertension, malignancy, pregnancy, acromegaly, leukemias, polycythemia and infections. On the other hand, a lowered basal metabolism may be present in the anemias, Addison's disease, many skin diseases, tumors of the pituitary gland and in diabetes.

Thyroid Insufficiencies.—The physician receives little help in identifying myxedema or cretinism from basal metabolism determinations. The clinical picture is characteristic and unmistakable. The basal metabolic rate is usually 30 per cent or more below the normal average. A basal metabolic rate of -40 per cent is considered to indicate a total lack of thyroid activity although as low as -59 per cent has been reported. Supplying the needed hormone by the administration of one of the several thyroid preparations can be successfully and safely carried out if reasonable care be exercised. A certain comfort, however, is derived from following the effect of treatment with basal metabolic rates. Inconsistencies between the clinical picture and the basal metabolic rate do occur as the following case will illustrate. An unmarried woman of thirty-five presented a classical picture of myxedema. Repeated basal metabolic rate determinations were within normal limits, the lowest value being -11 per cent. Subsequent experience revealed the fact that with 6 grains daily of the Burroughs Wellcome preparation all signs and symptoms of myxedema disappeared although the basal metabolic rate never went above $+6$ per cent except on one occasion when the patient on her own account increased the daily intake to 8 grains. After two weeks she developed outspoken symptoms of hyperthyroidism, nervousness, sweating, and a rapid pulse. Her basal at this time was $+19$ per cent.

Situations more confusing and difficult are those met in patients with a low basal metabolic rate without the clinical features of myxedema. Some of these patients unquestionably have a diminished thyroid activity and are markedly improved following the administration of thyroid substance sufficient to bring their basal metabolic rate to within the normal range. Others either have a low basal metabolic rate normally or are

thyroidism. Two months later the basal metabolic rate was +59 per cent. After iodine administration the basal metabolic rate fell to —5 and —1 per cent with relief of constipation and a general betterment in sense of well being. In this case it may reasonably be assumed we were dealing with hyperthyroidism which would have escaped without the aid of the basal metabolic rate.

As opposed to the above case is A. K., a woman of thirty-four, admitted to the clinic May 18, 1933, complaining of nervousness following a stillbirth three years ago with a marked increase in symptoms during the past year and a loss of 27 pounds. Clinically there seemed to be no question of the diagnosis of hyperthyroidism. There was a distinct stare without exophthalmos, edema of the eyelids, a moderate symmetrical enlargement of the thyroid gland, an overacting heart with a rate of 96, and a fine tremor of the fingers. Contrary to expectations the basal metabolic rate was only +14 per cent. Because of the mild grade of the symptoms the slight enlargement of the thyroid gland and undoubtedly influenced by the low basal metabolic rate it was decided to try radiotherapy. Treatments were given three weeks apart. After the third treatment the basal metabolic rate was +32 per cent, and after the fifth +51 per cent, although clinically she has shown steady improvement. She is still under treatment and we anticipate the basal metabolic rate will fall.

Another patient illustrates the lack of parallelism between the basal metabolic rate and clinical impression. O. F., a colored domestic, age forty-three, widow, came under our observation July 24, 1930, with unmistakable hyperthyroidism clinically supported by the basal metabolic rate which was +55 per cent. Her basal metabolic rate determinations are reported in detail (p. 1165).

Were it not for the consistency of the several basal metabolic rate determinations, the accuracy of the observation might be challenged. There is a striking lack of correspondence between the basal metabolic rate and clinical condition. This case further illustrates the occasional lack of correlation between the pulse rate and basal metabolic rate.

Co.) 2 grains daily for two weeks, and, after two weeks' rest, iodine in the form of syrup of hydriodic acid, 30 minims daily for two weeks. This régime is carried out three or four times a year. If no change in the size of the gland occurs within a year or at least two years there is little likelihood such measures will result in any change. In our experience of several years at the Presbyterian Hospital it must be said that only an occasional instance of significant reduction in the size of the gland has been observed. This apparently is contrary to the experience of physicians practicing in the endemic areas where iodine administration is usually followed by a reduction in the size of the gland. A few patients of this type have come to us who have been given sufficient thyroid extract to produce a true exophthalmic goiter, a therapeutic procedure which cannot be too strongly condemned.

Hyperthyroidism.—As in thyroid deficiency the basal metabolic rate aids the clinician but little in the diagnosis of clear-cut cases of hyperthyroidism. The test is of service in following the course of treatment be it medical or surgical. There is a temptation on the part of physicians to lean too heavily on this test. The wise clinician will place equal importance upon the course of the disease clinically. It is perhaps most useful in judging the optimum effect of iodine administration in preparation for operation and following the effect of radiotherapy.

Occasionally patients are seen where there appears to be wide discrepancies between the basal metabolism and the clinical impression. A patient, A. L., a housewife of fifty-seven, entered the dispensary June 3, 1930, with the sole complaint of constipation. The physical examination revealed little except an elevated blood pressure 210/110 and a secondary anemia (Hgb. 58, red blood corpuscles 3,200,000). After six months' observation with liberal doses of iron ammonium citrate the blood improved (Hgb. 78, red blood corpuscles 4,400,000) but little progress was made with relief of constipation. The basal metabolic rate at this time was +38 per cent without any discoverable signs or symptoms of hyper-

heart disease, mitral stenosis and fibrillation, with a debatable element of hyperthyroidism since she had an enlarged thyroid and a basal metabolic rate of +25 per cent. Several weeks of rest with digitalis resulted in no marked improvement. A partial thyroidectomy was performed following which the cardiac situation improved rapidly. Six months after operation there was no cardiac symptoms although she was still fibrillating without pulse deficit.

Another case, L. C., a Chinaman of fifty-seven, entered the hospital January 1, 1933, complaining of swollen legs, palpitation, dyspnea and cough with occasionally blood-streaked sputum of three months' duration. He was an apathetic individual distinctly icteric, not suggesting hyperthyroidism in the least. The thyroid gland was slightly enlarged and possibly a slight stare noted in the eyes but no exophthalmos. His heart was large, without organic valvular disease, rate rapid and regular; his liver enlarged and tender; edema of the lower legs. He was considered to be a case of arteriosclerotic heart disease. On rest and digitalis for several weeks no significant improvement was made. A basal metabolism determination was made and found to be +52 per cent. Partial thyroidectomy was followed by slow but distinct improvement, the jaundice cleared and signs of cardiac decompensation disappeared. He left for China April 10.

The extraordinary benefit derived from partial thyroidectomy in patients similar to these just described has led Blumgart and Levine to reduce the level of metabolism in individuals with chronic heart disease but without hyperthyroidism by total ablation of the thyroid gland. Several cases are reported and the results give much promise. The period of observation has been too short to permit any definite statement concerning the advisability of so revolutionary a procedure.

One of the difficult problems with which the physician is frequently confronted is the differential diagnosis between psychoneurosis and hyperthyroidism. In many psychoneurotics the clinical picture is suggestive of hyperthyroidism. There may be a basal metabolic rate of +15 to +20 per cent.

Date.	Basal metabolic rate.	Pulse.	Remarks.
July 24, 1930	+ 55	80	Seen in Out-Patient Department. Operation delayed at patient's request.
August 19, "	+ 50	84	Admitted to hospital August 17th. Sodium iodide 0.1 Gm. daily started.
" 26, "	+ 51	100	Sodium iodide increased to 0.2 Gm. daily.
Sept. 3, "	+ 94	108}	Good clinical improvement. Sodium iodide discontinued. Lugol's 2 mls. daily.
" 4, "	+ 84	92}	
" 9, "	+ 40	108	Partial thyroidectomy Sept. 10, 1930.
" 18, "	+ 22	100	Made an excellent convalescence from operation.
" 22, "	+ 26	80	Discharged from hospital.
Feb. 27, 1931			Gained weight and doing housework. Not nervous, no palpitation or tremor.
August 21, "	+ 65	76	No evidence of hyperthyroidism.
Nov. 21, "	+ 68	88	No symptoms of hyperthyroidism.
August 19, 1932	+ 46	72	No discoverable enlargement of remnant of thyroid gland.
" 4, 1933	+ 40	68	Continued in excellent condition.

Heart Disease.—Since the introduction of basal metabolism determinations into clinical use a real advance has been made in bringing to light cases of hyperthyroidism masquerading as heart disease. The test has served to improve the keenness of the clinical eye. Many of the patients in this category have few or no discoverable signs of hyperthyroidism and appear to be suffering solely from heart disease. The patient is usually over forty, frequently fibrillating, with unmistakable evidence of cardiac failure. There is no exophthalmos, no enlargement of the thyroid gland, no nervousness, profuse perspiration or tremor yet the basal metabolic rate may be markedly elevated. Attention may be drawn to these cases by the poor response to digitalization. Following partial thyroidectomy the clinical improvement leaves no doubt as to the correctness of the diagnosis. Furthermore the pathologic laboratory demonstrates a hyperactive gland on microscopical examination. As an illustration of this condition the following case is reported. L. B., forty-seven, single woman, in domestic service entered the hospital October 20, 1932, complaining of dyspnea, palpitation, nervousness and insomnia. Her palms were not moist, there was no exophthalmos; the thyroid gland was moderately enlarged; the heart was enlarged with unmistakable signs of mitral stenosis. The rate was rapid and totally irregular. The diagnosis was rheumatic

the hyperthyroid and the inability to store it is due to the increased demand for food. It has been observed that the cholesterol of the blood is increased in hypothyroidism and decreased in hyperthyroidism. This fact is considered by Hurxthal of value as a differential diagnostic aid in puzzling cases but I have had no personal experience with it.

The enormous increase in heat production in hyperthyroidism means that an increased amount of food is needed for the patient. We hear the "high caloric diet" mentioned frequently in connection with the treatment of hyperthyroidism either surgically or medically. Many times the so-called "high caloric diet" as prescribed is inadequate. Numerous observations now confirm the fact that these patients require much more than the normal 10 or 20 per cent increase over basal requirements at rest. As much as 75 or 100 per cent increase over their basals may be necessary to maintain nitrogen equilibrium and bring about a gain in weight in the hyperthyroid patient. From a practical standpoint gain in weight answers the question whether the patient is receiving sufficient food. We have found the basal metabolic rate a useful guide in securing adequate food intake. It is usually possible by employing concentrated foods to get the patients to take twice as many calories as the basal metabolic rate calls for.

The rôle of iodine in the physiology of the thyroid is a fascinating topic but only a few practical phases of the subject can be mentioned. The place this element holds in the prevention of nontoxic hyperplasia of the thyroid gland and its value in preparation of toxic cases for operation are well established. The extent to which iodine reduces the basal metabolic rate is usually in direct proportion to the initial elevation. In 185 unselected cases we have studied at the Presbyterian Hospital the average drop in the basal after iodine administration when the level was between +20 and +30 per cent was 9 per cent; with an initial basal between +70 and +80 per cent the average drop amounts to between 35 and 40 per cent. The above observation served as a standard with which to compare the effect of diiodotyrosin

Each patient presents its particular situation and I know of no scheme by which a separation can be made with certainty. Without doubt many individuals have lost part of their thyroid gland unnecessarily and probably others have missed the opportunity of relief by operation. A large number of patients assigned to the group of psychoneurotics have normal basal metabolic rates so that any marked increase in basal should be viewed with suspicion. When doubt exists the patient with moderately increased basal should be closely observed in good circumstances, with rest and sedatives and frequent basal metabolic rates made to determine its persistence. In certain of these cases the effect of iodine on the basal is of considerable diagnostic aid. If the basal metabolic rate be lowered following the administration of iodine then iodine should be discontinued to determine whether the basal is to return to its original level. A repetition of the experiment is desirable. A drop in the basal metabolic rate with clinical improvement following iodine administration is certainly suggestive of hyperthyroidism. On the other hand when no reduction of the basal is observed in such a procedure we consider the evidence in favor of the absence of hyperthyroidism.

Malignant Disease and Thyroiditis.—The basal metabolic rate is of little aid in the diagnosis of malignant disease of the thyroid. Of twenty-four cases reviewed at the Presbyterian Hospital there were basal metabolic rates determined on twelve. In eight cases the basal was within normal limits, the remaining —17 and —23 per cent, +39 and +80 per cent. The same may be said of acute and chronic thyroiditis. All of the basals in the few cases we have observed, eight in all, have been within normal limits.

General Metabolic Considerations.—The effect of hyperthyroidism or hypothyroidism on the protein, carbohydrate and fat metabolism can be explained largely if not wholly on the basis of the increased or decreased level of heat production. With adequate fat and carbohydrate, protein minima correspond to those found in normals. There appears to be no difficulty in the utilization of carbohydrate on the part of

be considered when one contemplates the use of iodine therapeutically in toxic cases. The temporary effect of iodine makes it essential to reserve iodine for preoperative use. It is true that cases are reported, and I have seen such, demonstrating a control of the toxicity over long periods until spontaneous recovery occurs, but in my experience iodine has proved disappointing in the medical management of toxic goiter. The impression that once the iodine effect is obtained and the patient "escaped," little benefit may be expected in the subsequent use of iodine is not correct. After a period, one to four weeks, without iodine even though it has been administered over a several months' period we note satisfactory responses. It must be said, however, that the second trial often results in a less striking response.

Conclusion.—I have endeavored to point out in the foregoing remarks how a knowledge of the deviations from normal of the metabolism in hyper- and hypothyroidism may be of service to the clinician. One impression I hope to make. Laboratory tests of function are valuable aids when given their proper place and importance. They have increased our knowledge of disease and have contributed to our clinical ability. It must be remembered, however, that they often represent single components of a complicated system of dependent variables. The danger not only in diseases of the thyroid, but in medicine generally, is to become a slave to laboratory data and place too little reliance on good clinical judgment.

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which has been so enthusiastically recommended in the recent German literature as superior to the inorganic preparation in common use. Chemically diiodotyrosin would seem to be the precursor of thyroxin, moreover almost all of the organic iodine in the thyroid gland is in the form of either thyroxin or diiodotyrosin. On the hypothetical basis that these two organic iodine compounds normally are in equilibrium in the gland, hyperthyroidism might result when thyroxin is present in excess, hypothyroidism when diiodotyrosin predominates. Our chemical studies of normal and pathologic glands have failed to bring support to such a hypothesis. The claims made for the therapeutic use of diiodotyrosin is that it reduces experimental hyperthyroidism, known to be unaffected by inorganic iodine compounds; that it is effective in so-called "iodine refractory cases"; and that iodine escape is less frequent. In a study of thirty cases including three patients who had previously received iodine, we could detect no difference in the effect of diiodotyrosin and that observed with Lugol's solution and sodium iodide. The reducing effect on the basals was commensurate in both preparations, nor was any change produced by diiodotyrosin in the iodine refractory patients. Our clinical experience with diiodotyrosin appears to be consistent with observations made in the laboratory. When rabbits are given gram doses of diiodotyrosin about 10 per cent is excreted as inorganic iodine, the rest either unchanged or as a lactic acid derivative. When given in the therapeutic amounts of 100 mg. doses to patients a larger percentage may be broken down to give inorganic iodine.

A word of warning against the indiscriminate use of iodine may be ventured. We have already mentioned its use in the adolescent goiter and as a therapeutic aid in selected cases. Long continued use of iodine in patients with nodular glands occasionally transforms a nontoxic gland to a toxic gland. I know of no advantage to be gained in administering iodine to individuals with nontoxic nodular glands. The great value of iodine in bringing about remissions in the toxic glands, either diffuse or nodular, in preparation for operation must always

Physical Examination.—Significant findings were a bilateral exophthalmos of moderate degree, moderate smooth symmetrical enlargement of the thyroid, coarse tremor of the hands, scattered patches of vitiligo over the entire body.

Treatment and Course.—Basal metabolism on admission was plus 52. After rest in bed and the administration of Lugol's solution, ten drops three times a day for two weeks, the metabolic rate had dropped to plus 14. At this time a subtotal thyroidectomy was performed. Her postoperative course was uneventful. Her basal metabolism ten days after operation was ± 0 and has remained within normal limits since. Subjective symptoms have been relieved. She is still nervous at times when under excitement but her nervousness no longer causes her distress. This patient's course is illustrated from the standpoint of weight, pulse and metabolic rate by Fig. 216.

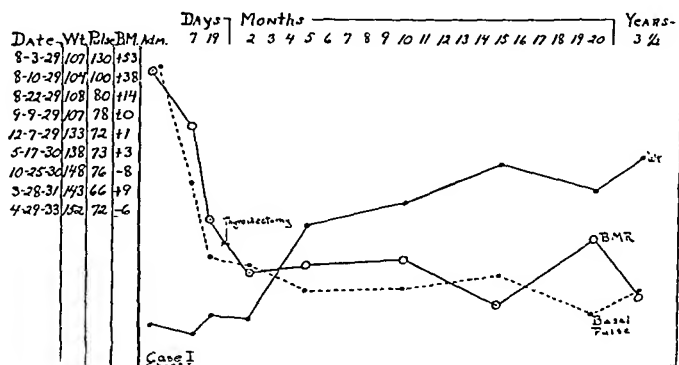


Fig. 216.—The course of a case showing the usual response to surgery as depicted by the weight, basal metabolism and basal pulse. The metabolism fell from plus 53 to plus 14 on iodine when thyroidectomy was performed. One month after admission the metabolism reached normal and has remained so since—a period of three and one-half years.

The result from surgical therapy in this case has been entirely satisfactory. The next case is described to illustrate cases belonging to a group in which prompt and permanent restitution of health does not occur and in which the result is not satisfactory.

Case II.—History.—A thirty-two-year-old male admitted first September 16, 1931. Chief complaint: Loss of weight. Six months before admission began to try to reduce by dieting because he weighed 192 pounds. After the loss of ten pounds he discontinued dieting but weight continued to diminish until on admission he weighed 112—a loss of 80 pounds. For six months he had noticed increasing nervousness, excessive sweating, loss of strength and a tremor of his hands. Three months before admission a physician had

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THE TREATMENT OF HYPERTHYROIDISM

HYPERTHYROIDISM may be treated medically by a régime of rest, high caloric diet, and the administration of nerve sedatives or by means of specific therapy such as surgery or x-ray. Fifteen years ago many medical men refused to admit that the surgeon restored the toxic goiter case to health any more promptly or surely than did they and were in fact reluctant to advocate surgery because of the operative risk involved. Since then the introduction of the preoperative preparation of patients with iodine has reduced the operative risk and the substitution of subtotal for conservative thyroidectomies has greatly improved the results from surgery. At present it is almost universally conceded that surgery offers the best hope of prompt and permanent restitution of health.

Prompt and permanent restitution of health is the ideal of any successful treatment. The intensity of the subjective symptoms in hyperthyroidism in the great majority of cases varies directly with the degree of elevation of the basal metabolic rate. The introduction of methods for easily estimating the metabolic rate has supplied an objective criterion by which the results of treatment may be judged and various methods of treatment compared. According to this reliable criterion surgery has proved itself the best treatment now available in the treatment of hyperthyroidism.

The case which we shall first describe illustrates the usual response of cases of toxic goiter to subtotal thyroidectomy.

Case I.—History.—White female, aged forty-two. Chief complaint, nervousness. Illness began ten months before admission. During this time she had been nervous and emotional, had frequent palpitation of the heart, and excessive sweating. Had steadily lost muscular strength and stair-climbing had become difficult because of weakness in legs. Despite increased appetite she had lost 18 pounds in weight. During her illness her eyes had become prominent.

end of this time he felt well, had gained $29\frac{1}{2}$ pounds and his basal rate was minus 5. He returned four month later stating that he had felt better until a few weeks previously when he had become nervous again. He had maintained his weight but his basal rate had risen again to plus 32. In the next two months he received five more x-ray treatments with relief of symptoms and a reduction in his basal rate to minus 4. He was last seen seven months later and has continued well with a basal rate of plus 9.

The course of this patient from the standpoint of pulse, weight and metabolism is shown in Fig. 217.

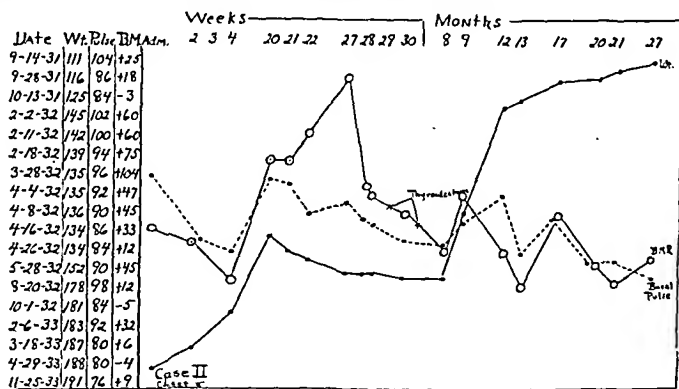


Fig. 217.—An unsatisfactory result from surgery, taking prompt and permanent restitution of normal metabolic rate and relief of symptoms as the criterion of successful treatment. Because of unusual features in the symptomatology and the development of an iodine-fast state operative treatment was delayed for seven months after first admission. The basal metabolic rate after thyroidectomy was plus 12 but rose again in one month to plus 45. For this continued hyperthyroidism the patient was given nine x-ray treatments in the next five months when symptoms were relieved and normal basal rate was again present. Four months later there was a return of symptoms when he was given five more x-ray treatments. He has now been free from symptoms for eight months, his basal rate is normal and he has regained his original weight.

Comment.—As regards special comment relative to these individual cases attention is drawn, in the first case, to the scattered patches of vitiligo, or depigmented areas of skin, on the patient's body. This is not an infrequent occurrence in cases of hyperthyroidism and the condition persists after cure of the hyperthyroidism. In the second case there was present, on his first admission, a severe hypochromatic anemia. In our experience there is no relationship between hyperthyroidism

advised tonsillectomy which was performed and he had made an uneventful recovery but without relief of symptoms.

Physical Examination.—Exophthalmos, both eyes. Moderate, smooth, slight, symmetrical enlargement of thyroid, coarse tremor both hands, basal pulse 104. Basal metabolism on admission plus 25, one week later, plus 18. An unexpected finding was a marked secondary anemia; red blood cells, 2,850,000; hemoglobin, 50 per cent. The patient was given one 500 cc. transfusion and received liver extract and Bland's mass by mouth. A month later his red blood cells had risen to 4,100,000 and his hemoglobin was 76 per cent. A month after admission his weight had risen from 111 to 125 pounds, at which time his basal rate had fallen to minus 3. He had received ten drops of Lugol's solution three times a day for five days before this test was made. At this time the advisability of a thyroidectomy was considered. Since the patient presented an unusual feature in his anemia, in the face of the relatively low metabolic rate, and the improvement in symptoms and weight it was decided to defer operation and observe his further course. It was considered that he might have arrived at a spontaneous cure or remission in his thyroidism.

Patient was admitted a second time two and one-half months later. For six weeks after his discharge he had been much improved, then his appetite began to increase, he began to lose weight, and nervousness began to distress him again. Despite his story of weight loss his weight was 20 pounds above his weight at discharge. On examination his exophthalmos was more marked, the thyroid was more enlarged, and the tremor greater than on first admission. His red cells were 4,100,000, hemoglobin 81 per cent.

One month before present admission his physician had prescribed two drops of Lugol's solution for him three times a day, which he had continued. His basal metabolism was now plus 60. It was thought probable that the patient was now in an iodine refractory or fast state but the iodine was continued in hopes that a remission might occur. No further remission occurred however and at the end of two weeks his symptoms had increased and the basal metabolic rate had risen to 75 per cent. It was decided, out of consideration for the patient's safety, that it would be better to operate upon him during an iodine remission. His iodine was therefore omitted for one month. By this time his metabolism had risen to plus 104. The iodine was then resumed and in nine days the rate had dropped to plus 45.

At this time, on April 11th, the first stage of a thyroidectomy was done by Dr. M. K. Smith with the removal of the right lobe and on April 18th the subtotal thyroidectomy was completed. Dr. Smith found the weight of gland removed was 66 Gm. and estimated the remnant as 9 Gm. His metabolism ten days following operation was plus 12 and he was discharged to the convalescent hospital much improved. He returned for follow-up one month later. He had gained 18 pounds in weight but it was obvious that there was a persistent hyperthyroidism. He still complained of nervousness. Tremor and tachycardia were still present. Examination of the neck showed hypertrophy of the thyroid remnants on each side. The question of a recurrent thyroidectomy or treatment with x-ray was discussed and he elected to have x-ray. In the next five months he had eight x-ray treatments. At the

months for the first year after operation and twice a year thereafter. This is not always easy to do since many patients, if they are still well, feel no incentive to return and others move to other localities. We have accomplished such a follow-up in 132 operated cases in which one to four years have elapsed since operation. The following is a summary of the results:

83 per cent had prompt relief and have required no further treatment.

14 per cent have required further treatment for hyperthyroidism:

3 had secondary operations—results good in 2, unknown in 1.

12 had postoperative x-ray, good results in 11.

4 were controlled by iodine therapy.

3 per cent received thyroid therapy after operation.

In our hands therefore we believe the patient has an 83 per cent chance of prompt restitution of health from surgical therapy. As far as we know there is no way of telling in advance whether an individual case does or does not belong to the group in which the result will be satisfactory. We have been unable to establish a relationship between satisfactory or unsatisfactory results and the duration of the disease, metabolic rate, age of patient, intensity of symptoms or the micro-pathology of the excised gland. The unknown stimulus, which in the first place acted to cause the thyroid gland to hypertrophy and to oversecrete, in the unsatisfactory cases seems to persist with sufficient vigor to cause regeneration of the gland remnants.

The x-ray treatment of hyperthyroidism has many enthusiastic advocates among roentgenologists. We have used this method of therapy in a comparatively small number of cases of which the following is an example:

Case III.—History.—Patient was a sixteen-year-old white female admitted November 7, 1930. Her chief complaint was headache which began four months before admission. These headaches increased in frequency until they occurred about once a week. They were associated with nausea and vomit-

and anemia. In this case no cause for the anemia was determined. The patient's appetite had been very poor while the usual toxic goiter case has an excessive appetite. It is also interesting to note that this patient had had a tonsillectomy performed without untoward reaction. There is considerable hazard in subjecting a case of hyperthyroidism to surgical procedure until the toxemia has been interrupted and numerous cases are reported of fatal thyrotoxic crises having been precipitated by such procedure. Certainly no operation of election should be performed on a thyrotoxic case without first inducing a remission of symptoms by the administration of iodine. At this time such cases will stand operative procedure with greater safety but the correct policy is to delay any operation of election until the thyrotoxicosis has been cured. This case also illustrates a phase of the problem of iodine administration. Iodine administration produces a remission of symptoms in the toxic thyroid case in from six to ten days. If the iodine is continued its effect is lost and no further remission occurs while the iodine is continued. The patient is said to become iodine-fast or refractory. To obtain remission again the administration of iodine must be interrupted for a period, usually a month, when its readministration again results in a remission. On his second admission the patient had received iodine for a month. Continuation of the iodine resulted in no remission but after a month without iodine a very satisfactory remission was obtained.

Case I represents a satisfactory result from surgery—prompt and permanent restitution of health after operation. Case II represents an unsatisfactory result—continuation of the hyperthyroidism after thyroidectomy. What can a thyroid patient be told as to the prospects of his obtaining a satisfactory result, such as that obtained in Case I, in his individual case?

The answer to this question is to be found in the experience gained by a careful follow-up of a reasonable number of cases. Our own endeavor in the follow-up of cases has been to examine them and to obtain their metabolic rates every three

Comment.—The satisfactory result in this case raises the question as to the necessity for subjecting the patient to the ordeal of surgery. The answer to this question rests upon the frequency with which such a result is obtained and the comparative time required to obtain a restitution of health.

Our own experience has not been a sufficiently large one from which to draw conclusions. Twenty-one cases have received radiotherapy under careful observation. Of these in 19 the toxemia was ultimately controlled as indicated by restitution of normal metabolic rate and the relief of symptoms. In the successful cases the average number of treatments was 24.7, the maximum number 37 and the minimum 10. The average duration of treatment was 12.1 months with a minimum duration of 3 months and a maximum of 14 months.

Pfahler and Vastine¹ report the treatment of 361 cases by irradiation. Of these they report 56.9 per cent cured, 30.9 per cent markedly improved and 12.2 per cent not improved.

In our own cases the average time required to obtain restitution of normal metabolic rate was a little over one year. In a disease in which we know a considerable number of cases progress to a spontaneous cure or remission the influence of the therapeutic agent which requires so long a time to effect a cure is open to question. However we feel from statistical comparisons that more cases eventually are restored to health with x-ray treatment than go on to spontaneous cure without specific therapy. The reason for the popularity of surgery over irradiation in the treatment of hyperthyroidism is that it accomplishes restitution of health much more quickly. Prompt restitution of health is important not only from the economic standpoint but because a long continued toxemia exposes the patient to permanent myocardial injury and the dangers of a thyroid crisis. It seems to us that x-ray therapy has a place in the treatment of mild cases kept under frequent observations and we have the impression that it is particularly useful in the cases in which there is a continuation after thyroidectomy of a mild toxemia such as occurred in Case II.

¹Transaction American Association for the Study of Goiter, p. 177, 1932.

ing and compelled her to go to bed. They were bitemporal in character. Between headaches she noticed lack of energy and she had lost 36 pounds in nine months—140 to 104 pounds. Appetite had been increased.

Significant physical findings were: Prominence of eyes; a stare rather than a definite exophthalmos; moderate symmetrical enlargement of thyroid over which a bruit was heard; coarse tremor of hands, and a basal pulse of 90. Her basal metabolic rate was plus 41 on admission and plus 40 one week later. She was given ten drops of Lugol's solution three times a day with the expectation of treating her by thyroidectomy. Eight days later the basal rate had fallen to plus 13 with corresponding improvement in symptoms. Operation was refused by her family and she was instructed to report to the

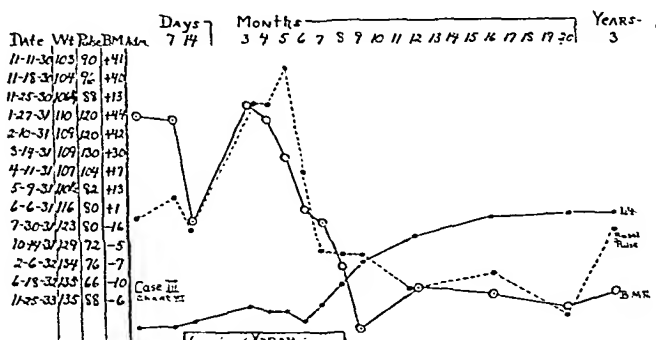


Fig. 218.—A case treated by x-ray admitted to the hospital with the expectation of surgical therapy. Metabolism dropped from plus 40 to plus 13 on iodine. Refused surgery. Iodine was omitted and x-ray treatment begun. On omission of iodine, basal metabolic rate rose again to plus 44. In the next six months received twenty x-ray treatments. At the end of this time the rate average had reached normal and symptoms had been relieved. She had been well since last treatment, two years ago. In our own cases the average duration of x-ray therapy has been one year. In this case the x-ray dosage was 200 R units at each treatment to alternate sides of neck.

clinic for observation and to the radiotherapeutic department for treatment. Iodine administration was stopped. She returned two months later when her basal rate had risen again to plus 44. In the next six months she received 20 x-ray treatments and at the end of this time she was without symptoms, her headaches had disappeared, her basal rate was plus 13, and no thyroid enlargement was present. She has remained well since. Her course is illustrated in Fig. 218.

The distinctive feature in this case was the complaint of periodic headache. We have encountered several thyrotoxic cases in which periodic headache has been a prominent complaint which disappeared after the interruption of the toxemia.

testing of excretory ability. It is diffusible, and is found, in all the fluids of the body outside the kidney, in approximately uniform concentration. Its excretion is therefore not interfered with by unusual distribution or storage, such as the storage of sodium chloride in edema fluids. It is continually produced, and therefore artificial administration is unnecessary. And it is easily, quickly, and accurately determinable by analysis, which is a matter of importance.

Changes in the behavior of urea have been observed in connection with renal disease since the time of Bright. Such changes are: (1) decreased concentration of urea in urine; (2) increased concentration of urea in the blood as the result of retarded excretion; (3) decrease in the excretion rate of urea compared with the concentration in the blood. In tests based on this decrease, both blood concentration and excretion rate are taken into account, and the results have been more significant than those of observations in which either blood alone or urine alone is examined. Such comparison tests were first introduced by Ambard in 1912.¹ His rather complicated formula for expressing the comparison has, as the result of later work, been replaced by simpler and more accurate ones.

Marshall,² Addis,³ and others have shown that if a high diuresis is maintained the amount of urea excreted per minute will equal that contained in a constant volume of the subject's blood; this volume in a normal adult is about 75 cc. If the urea concentration in the blood is doubled the urea excretion rate is also doubled, so that the excretion per minute still represents the urea content of 75 cc. of blood. If the urine volume sinks below 2 cc. per minute, the urea excretion sinks, but a correction for low urine volumes was introduced by Austin, Stillman and Van Slyke,⁴ so that it is not necessary to limit observations to periods of high diuresis. Doctors Rhoads, Hiller, Alving, and myself,⁵ working with animals, have found that if the blood flow through the kidneys is cut down, the rate of urea excretion is decreased proportionately to that of the blood flow.

CLINIC OF DR. DONALD D. VAN SLYKE

THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH

TESTS OF RENAL FUNCTION IN BRIGHT'S DISEASE

THE kidney has many activities. When disease causes progressive destruction of the organ, each of its activities must sooner or later be retarded. The degree of retardation may indicate with more or less accuracy the advance of the disease, and thereby serve as a functional test.

Among the known activities of the kidney are the excretion of water and the various solids of the urine, the concentration of certain of these solids to such an extent that some of them, such as urea and creatinine, may be 50 to 100 times as concentrated in the urine as in the blood, the formation of the urinary ammonia, which Nash and Benedict have shown occurs in the kidney, and the conjugation of glycine and benzoic acid to form hippuric acid.

Retardation of each of these natural activities has been used as a measure of renal damage. In addition many tests have been based on the excretion of administered substances which do not occur among the natural metabolites. Such tests are those with methylene blue, phenol red, sulphocyanate, iodide, and noncombustible sugars, such as xylose. Other tests have been based on excretion of natural metabolites, such as salt, urea and creatinine, but after the amounts of these substances in the body had been artificially increased by administration, either by mouth or parenterally.

It has been one of the problems of the clinic for renal disease in this hospital to study functional tests in patients under close and prolonged clinical observation, in order to ascertain which tests were most sensitive, reliable, and capable of practicable application and definite interpretation.

Without reviewing the experiments made with other substances, endogenous and administered, I may say that we have come to consider urea as the one best suited for the practical

Figure 219 represents a case of acute hemorrhagic Bright's disease with complete recovery. When the patient was first observed the urea clearance was only 15 per cent of normal, but within two months it rose to the normal range. The patient was discharged in the fourth month. At the time of her

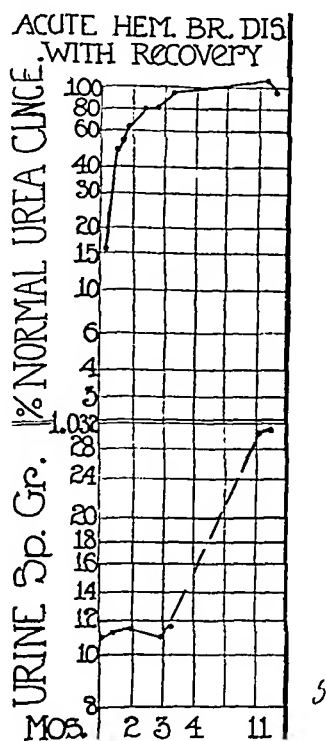


Fig. 219.—Recovering case of acute hemorrhagic nephritis. Changes of urea clearance and of urine specific gravity in Addison concentration test. Note that three months after onset the clearance had returned to full normal value, while specific gravity test still showed no improvement. Eleven months after onset both tests were normal. (Alving and Van Slyke, unpublished.)

return six months later not a trace of anything to indicate the presence of renal damage was found.

Figure 220 illustrates the way in which the urea clearance behaved in a case of acute nephritis which at first improved in a way to promise recovery, but did not attain a stable restoration. There followed a chronic nephritis with a gradual

In advanced Bright's disease there is a great diminution of the "urea clearance," by which term is meant the volume of blood cleared of urea by excretion in one minute. The average normal man who excretes per minute urea equal to that contained in 75 cc. of blood, has a urea clearance of 75 cc. In contrast the nephritic in uremia shows a urea clearance of only 3 or 4 cc. of blood per minute. We have found it convenient to express this urea clearance in terms of percentage of the average normal. In a nephritic patient approaching uremia the clearance is only about 5 per cent of normal. So nearly as one can tell by examination of the glomeruli of the kidneys obtained at autopsy, the fall in clearance is proportional to the decrease in functioning glomeruli.^{6, 7} Urea clearance can fall to 10 per cent, and sometimes less, of normal without confinement of the patient to bed, provided his condition is not complicated by general circulatory disease or by edema.*

* The technic of determining the urea clearance is fairly simple. It requires collecting the urine during two measured time intervals of approximately an hour each, and taking a blood sample at about the middle of the two-hour period. The volumes of the urines are measured and urine and blood are analyzed for urea. It is desirable, although not necessary, to have the subject drink one or two glasses of water before the test in order to have a fairly liberal flow of urine. Incomplete emptying of the bladder is the chief source of error, and its effect on the results is less if the urine volume is high.

If the urine volume exceeds 2 cc. per minute the clearance is calculated by the formula:

$$\text{Per cent of average normal clearance} = 1.33 \frac{UV}{B}$$

If the urine volume is less than 2 cc. per minute the calculation is by the formula:

$$\text{Per cent of average normal clearance} = 1.85 \frac{U\sqrt{V}}{B}$$

The introduction of the square root of V into the formula for low urine volumes corrects for the retardation of urea excretion which accompanies fall of the minute volume below 2 cc. per minute. U and B represent urea concentration in urine and blood, V represents urine flow in cubic centimeters per minute.

For a more complete discussion of the clearance and the correction for body size used with children, see p. 564, vol. II, Quantitative Clinical Chemistry of Peters and Van Slyke, or the original papers.¹⁷

lost in the urine. The subject, freed from edema, feels better for some time than he did when his renal function was actually greater. However, the continued fall of the clearance shows that uremia is approaching, as in this case when death occurred twenty-eight months after the onset of the acute nephritis, and sixteen months after the clearance sank below 20 per cent.

We have not limited our studies of functional tests to the urea clearance, but have experimented with various others in order to compare their sensitivity, reliability, and simplicity.

Of these tests, the "concentration test" based on the ability of the kidneys to excrete urine of high specific gravity, has shown itself to be especially sensitive to renal damage and particularly simple to carry out. In 1898, Koranyi pointed out that the kidney does thermodynamic work in concentrating urea and other solids in the urine to many fold their concentrations in the blood. The amount of urea contained in 50 liters of blood, for example, is likely to be concentrated into 1 liter of urine. It takes about as much calculated work to do this as to compress 6 liters of gas at atmospheric pressure into 1 liter at 6 atmospheres. A damaged kidney cannot accomplish this concentration. Later investigators who applied this principle found that although, theoretically, it is better to use the freezing point in their calculations, it is more practicable to use specific gravity, and the results are about as significant. The results of the test vary according to the régime followed by the patient. It is necessary that the urine be passed under conditions which will favor high concentration and specific gravity. Addis⁸ in San Francisco, and Newburgh and Lishmet⁹ in Ann Arbor, have in recent years made especially careful studies of concentration tests.

Dr. Alving in this clinic has also made a study of these tests carried out over a period of several years, during which he has compared them with the urea clearance and other tests in patients of various types observed for long periods. The concentration test upon which he finally settled is that developed by Addis. The patient consumes a dry diet for

fall in urea clearance, which at the end of twelve months was only 20 per cent of normal.

Very often the character of the disease changes at this point. Until the falling clearance in a chronic case reaches about 20 per cent of normal, edema is likely to be the most obvious factor of the disease and the one chiefly responsible

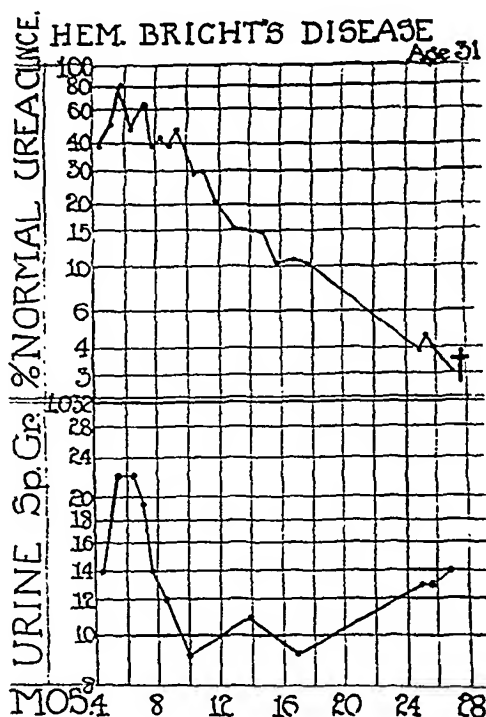


Fig. 220.—Case of acute hemorrhagic nephritis with temporary improvement, followed by lapse into progressing chronic nephritis with eventual death in uremia. (Alving and Van Slyke, unpublished.)

for incapacitating the patient. As kidney function diminishes toward 20 per cent, however, this edematous stage, for some reason, is apt to pass. The plasma proteins are likely to increase with a coincident tendency of the edema to diminish. Perhaps the gradual destruction of the excretory elements of the kidney diminishes the amount of albumin

Then during two months it rose to 100 per cent. The specific gravity, which was very low at 1.010, showed no rise at all during these two months. The improvement in this patient was genuine, and was followed by complete recovery. The specific gravity figures six months after discharge from the hospital were also found to be normal. For some time after the second month an abnormality remained in the kidneys which, although it did not interfere with urea excretion, was nevertheless indicated by the low specific gravity values which the concentration test continued to yield.

In Case II during the first seven months (Fig. 220) the gravity test followed the urea clearance more or less closely. But between the seventh and tenth months the gravity fell to 1.010, which is nearly the minimum reached in terminal nephritis. The urea clearance still showed 30 per cent of normal function. During the subsequent twenty months, while the clearance gradually approached the uremic level at 5 per cent of normal, the specific gravity showed no further fall.

Other cases showed similar results; they indicate that the specific gravity test is extremely sensitive in revealing slight renal damage, but that it does not distinguish between a moderately advanced and a terminal stage of the disease.

We have also compared the results of the urea clearance test with the simple determination of the blood urea and of the blood creatinine. A normal blood urea is anything below 23 mg. of urea N per 100 cc. of blood, while the normal blood urea clearance under the conditions in which we work is 70 per cent or more of the average normal. Figure 221 represents the results of observations in this clinic.¹⁰ In many cases when the urea clearance definitely indicated that there was kidney damage, the urea content of the blood was normal. Only after renal destruction has proceeded so far that the urea clearance is less than 20 per cent of normal does one always find a high blood urea. The blood urea, determined by itself and without relation to the urea excretion, may be normal until the terminal stage of the disease, as we have defined this stage.

Figure 222 presents a comparison of the creatinine con-

twenty-four hours. That is, for the twenty-four hours following breakfast on a given morning he is allowed no liquids or liquid food. During the last twelve hours of the twenty-four-hour period, the twelve hours of the night, the urine is collected, usually totaling 300 to 600 cc. in volume. The specific gravity is noted and urine is centrifuged for a quantitative Addis count of the formed elements, which we routinely do in connection with the specific gravity observation. The protein content of the urine is also determined, and a correction is made for its effect on the specific gravity. Since 1 per cent of protein raises the specific gravity by 0.003, this correction is often important. The normal person excretes under the conditions of this test urine which has a specific gravity usually above 1.026. If the kidneys are so damaged that they have lost their ability to concentrate, the specific gravity is always lower. A single test cannot be relied upon, because sometimes a normal subject will excrete, for undetermined reasons, urine with an unusually low gravity. If the conditions of the test are followed, however, anomalous results are rare.

We have found that the ordinary specific gravity bulb is not accurate to the third place. For the purpose of determining specific gravity to the third decimal we use a modified Westphal balance, a balanced beam which has a solid glass cylinder of 10 cc. volume suspended at the end.* A sliding weight on the beam is so arranged that when the weight is at the zero mark and the cylinder is immersed in distilled water a balance is obtained. If the specific gravity is above 1.000 the weight is moved out along the scale until balance is regained. The scale reads directly in specific gravities. The lower curves in Figs. 219, 220 represent the results obtained by the specific gravity method in the two cases described. A comparison of these curves with the urea clearance curves above them indicates the relative behavior of the two tests.

In Case I (Fig. 219) the clearance was first noted one month after acute onset, at 15 per cent of average normal.

* This balance was made from an ordinary Westphal balance for us by Eimer and Amend, of New York.

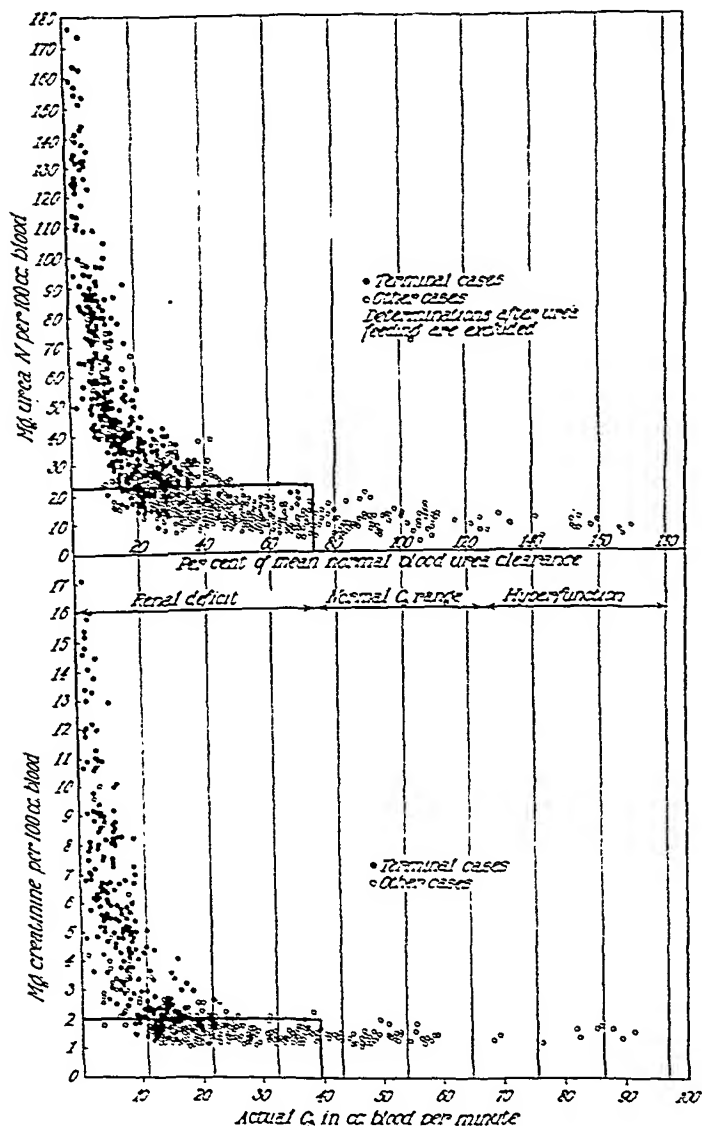
Then during two months it rose to 100 per cent. The specific gravity, which was very low at 1.010, showed no rise at all during these two months. The improvement in this patient was genuine, and was followed by complete recovery. The specific gravity figures six months after discharge from the hospital were also found to be normal. For some time after the second month an abnormality remained in the kidneys which, although it did not interfere with urea excretion, was nevertheless indicated by the low specific gravity values which the concentration test continued to yield.

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Figure 222 presents a comparison of the creatinine con-



Figs. 221, 222.—Comparison of urea clearance values with blood urea and blood creatinine contents in cases of Bright's disease. The rectangle in the lower left corner of each chart encloses observations in which the clearance was pathologic, while the blood urea or creatinine remained normal. C_s indicates standard urea clearance, estimated for urine output of 1 cc. per minute (Van Slyke, McIntosh, Möller, Hannon and Johnston, *Journal of Clinical Investigation*, vol. 8, 1930).

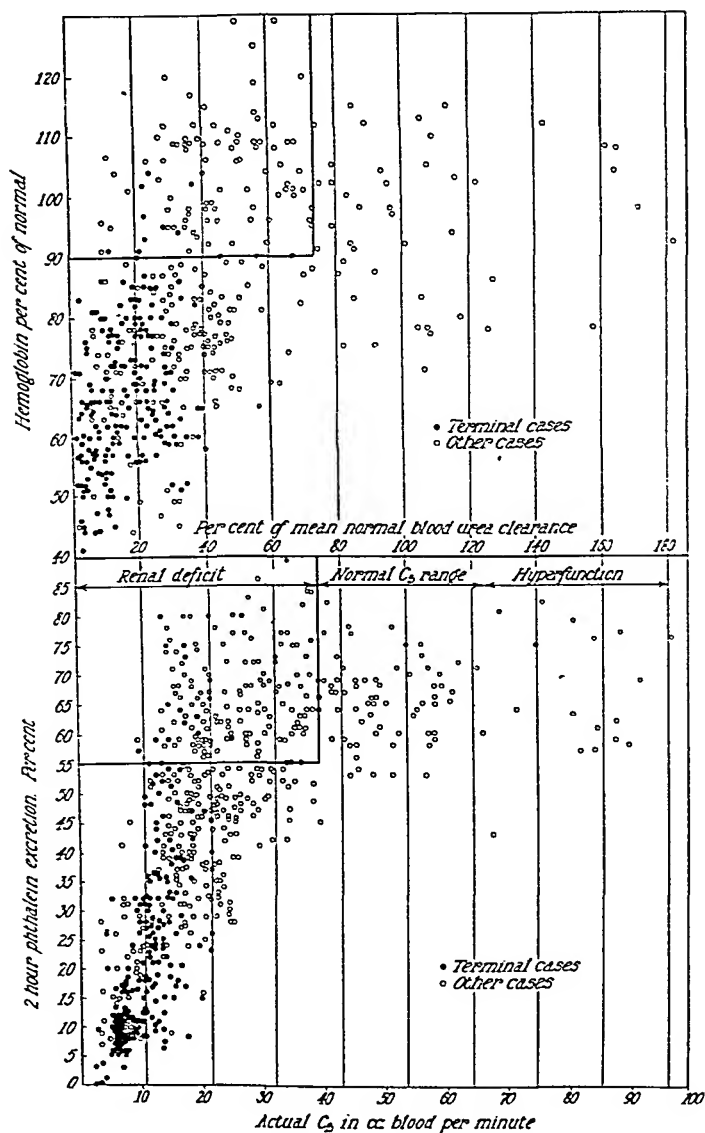
Because the phthalein test, as previously performed, proved less sensitive and reliable than the urea clearance, we have for several years ceased to use the phthalein routinely. It has, however, proved of especial value in cases of bladder retention when carried out with the clearance. In such cases only a few per cent of injected phthalein may be excreted in an hour without catheterization, because the greater part remains in the bladder. The urea clearance, on the other hand, though unusually variable, indicates more nearly normal function. In a case, for example, which shows in an hour only 5 per cent of phthalein output, but gives urea clearances varying between 30 and 90 per cent of normal, retention is highly probable.

The value of a kidney function test in the study of renal disease depends to a large extent upon two factors:

1. The inherent reliability of the test in terms of the sensitiveness with which it reveals renal damage, the quantitative reproducibility of its results, and its immunity from unpredictable extrarenal influences.

2. The body of accumulated observation available to assist in interpreting the results of the test. In order that an inherently good test achieve its full usefulness, it must have been systematically tried in numbers of renal cases of different types, with observations throughout the initial, chronic, and terminal stages of each type. The more complete the body of observation thus gathered, the more accurately in a given case can one use the results of the functional test to assist in diagnosis and prognosis.

At present, on the basis of its standing on these two factors, we depend chiefly on the urea clearance in the diagnosis and prognosis of our cases. We know from systematic observations carried on during the past 12 years⁶ that in *chronic* Bright's disease a steady fall in the clearance indicates a steady decrease in the amount of functioning renal tissue, and that, when the clearance falls to 5 per cent, uremia is near at hand, regardless of the type of the hemorrhagic, degenerative, or other type that in



Figs. 223, 224.—Comparison of urea clearance values with blood hemoglobin contents and phenolsulphonephthalein excretions in cases of Bright's disease. The rectangle in the upper left corner of each chart encloses observations in which the clearance was pathologic while the hemoglobin or phthalein remained normal (Van Slyke, McIntosh, Möller, Hannon and Johnston. Journal of Clinical Investigation, vol. 8, 1930).

In studying the condition of a patient with Bright's disease, our results have indicated that the performance of a multiplicity of tests is unnecessary. It appears that the urea clearance, supplemented by the concentration test in cases where the clearance is found normal, will yield all the information useful for diagnosis and prognosis that is at present obtainable by quantitative measures of renal function. We do not mean that other tests, now known or due to appear in the future, may not give equally reliable information. The creatinine clearance, for example, appears to duplicate the information with regard to renal damage yielded by the urea clearance. If improvements in the technic of the creatinine clearance should later make it the more practicable of the two, it could then well replace the urea clearance. There would, however, appear to be no object in using both. At present we have come to rely routinely in our clinic upon the urea clearance and the gravity test, because they combine simple technic and definite interpretations through the different stages of renal disease. Addition of a third test would appear justified only if it yielded some specific type of information concerning the progress of the disease which is not afforded by either the gravity or the clearance.

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acute nephritis, on the contrary, the clearance may fall nearly to the uremic level, and that nevertheless complete recovery may occur. Such recovery is rare, however, unless the clearance begins to rise within four months after the acute onset.⁶ We believe that if we could find any régime which in the chronic disease would check the steady clearance fall exemplified in Fig. 220 we could arrest the progress of the disease. We believe, on the other hand, that régimes which do not arrest the fall of the clearance can be branded as valueless, except as palliatives.

A normal clearance does not necessarily prove the absence of renal disease. In cases recovering from acute hemorrhagic disease the clearance frequently regains a normal level while one or more other signs, such as microscopical hematuria, albuminuria, or edema, still persist in some degree. Such a case cannot be considered to have completed its recovery until these signs of renal pathology have also disappeared. Usually if the clearance regains normality, disappearance of the other signs occurs at the same time or later. But sometimes, as in the case shown in Fig. 220, complete healing does not follow, the disease becomes chronic, and the clearance shrinks again. This time the shrinkage indicates irreversible destruction of glomeruli.

The creatinine clearance, which is determined in the same manner as the urea clearance, but is assumed by Rehberg¹⁵ to be a measure of the glomerular filtrate, has been found by Hayman, Halsted and Seyler¹⁶ to parallel the urea clearance, but to be less practicable because of the greater difficulty of accurate creatinine analyses.

It appears from Alving's results that the *specific gravity concentration test* may serve to supplement the urea clearance by assisting one to decide whether, when the clearance has returned to normal, the disease has completely disappeared, or has merely become latent. In such cases it appears that the concentration test is more likely than the urea clearance to remain below normal until disappearance of renal pathology has approached completion.

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the end. On the other hand, if the patient's general condition is overlooked, in a hopeless attempt to treat the kidneys, invalidism may be unnecessarily brought on months or years before it is necessary. This viewpoint has already been expressed by Peters and Van Slyke,² Addis,³ McCann⁴ and Butler.²¹

I do not aim to present new experimental work, but to stress the soundness of the present views, as shown by our experience in the treatment of chronic Bright's disease during the past ten years.

From the historical standpoint, it may be said that the more liberal use of protein in the diet owes its beginning to the conception of "nephrosis" by Mueller in 1905.⁵ This conception led Epstein⁶ to advocate the use of a high protein diet in "lipoid nephrosis" as early as 1917. Since then protein has been fed in large quantities in degenerative Bright's disease (nephrosis) but the value of a liberal protein intake in the other forms of Bright's disease has only gradually been recognized.

Epstein⁶ first also conceived of the lowering of the plasma proteins as the cause of edema in nephrosis, basing his deduction on the relationship of the plasma proteins to edema previously demonstrated experimentally by Starling.⁷

All causes of low plasma proteins in nephrosis are not known, but certainly the following factors play a large part; first, loss of protein (chiefly albumin⁸) through the kidneys; second, malnutrition whether due to anorexia, digestive disturbances, or to the disease itself; third, increased protein catabolism due to concurrent febrile infectious diseases. In addition there may be another factor, namely, a faulty mechanism of plasma protein synthesis or regeneration, but of this we know very little. The latter factor may be of importance in the last case to be presented. At any rate, in view of the importance of the other factors, it does not seem logical to treat degenerative Bright's disease (nephrosis) by means of a low protein diet. The folly of this is emphasized further by both clinical and experimental evidence that a low protein diet

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THE DIET IN CHRONIC BRIGHT'S DISEASE

THE older treatment of chronic Bright's disease stressed the kidneys. The diet in almost universal use in all stages of the disease was low in protein and low in salt content. The reason for protein restriction was that the diseased kidney has a diminished ability to excrete the waste products of protein catabolism and the resulting nonprotein nitrogen retention occurring in the later stages of the disease increases with the progress of the disease. It was supposed that the burden on the diseased kidney could be lessened by limiting the protein intake and it was hoped that healing processes would by this means be aided. An added reason for limiting protein was the general belief that the products of protein catabolism have a detrimental effect on the kidney. Salt was limited because it was the common belief since the work of Widal¹ that in the edematous stages of Bright's disease the edema is due to the failure of the kidney to excrete salt. We now ascribe the edema chiefly, if not entirely, to extrarenal causes.

In this clinic we no longer aim to arrest the progress of the disease by diet, because all the years of experience with therapeutic diets have failed to give evidence that any such therapy will influence the progress of the lesions in the kidney. We try, on the other hand, to treat the patient and his general symptoms, the chief of which are edema, malnutrition and wasting. We have no reason to believe that we can either cure, or even check, the chronic disease by diet. But good treatment of the general physical condition will often keep the patient active and subjectively well until within a few weeks of

is given without salt, it is excreted without difficulty, and the diuresis may favor salt excretion and edema reduction. Limitation of water in these patients produces unnecessary suffering from thirst. It also reduces urine output to volumes below those at which renal excretion of solids is best (*e. g.*, with a urine volume of 0.5 cc. per minute urea is excreted only half as rapidly as when the volume is 2 cc.).

In the chronic active stage of hemorrhagic Bright's disease (glomerulonephritis), with nephrotic type of edema and renal impairment the treatment is the same as in degenerative Bright's disease. Even in the presence of low kidney function we have not found that protein restriction is advisable. It must be remembered that this is as a rule a wasting disease and there is need for protein to replace the body proteins that are lost. It was observed by Peters, Bulger, Lee and Murphy¹⁰ and later by Keutmann and McCann¹¹ that on high protein diets emaciated patients with nephritis can store large amounts of nitrogen while they gained weight due to increase in tissue. In the adult other conditions under which a positive nitrogen balance can be maintained for a prolonged period of time occur following starvation or convalescence from a wasting disease as well as during and after pregnancy. These are conditions during which the need for tissue building is obvious. Proteins so stored cannot possibly cause a burden on the excretory function of the kidneys. It has been our experience that a liberal protein intake does not have any detrimental influence on the course of hemorrhagic Bright's disease. Instead, as illustrated by the first case we are going to present, it may have a beneficial effect on the replacement of body tissue and the shortening of convalescence, particularly if the patient has formerly been on a very low protein diet.

During the latent stage of hemorrhagic Bright's disease and during the chronic active stage in patients where there is no edema and in whom the plasma proteins are normal or nearly normal, and the albuminuria is below 1 Gm. per day, we allow the patients to be unrestricted in their choice of food, provided only that their diets meet the same requirements

can, in itself, produce low plasma proteins and edema in previously healthy subjects. There is also some evidence that the anemia which often occurs in the course of Bright's disease is aggravated by the use of a low protein diet.

The diet in nephrosis should contain enough protein to replace that lost in the urine, and that lost due to destruction of protein during febrile or infectious illnesses, and in addition an amount (for safety calculated as 1 Gm. per kilogram) necessary to maintain nitrogen equilibrium in a healthy subject. In the presence of malnutrition there is further need for protein in replacing wasted body tissues. The diet should be high in calories and they should be supplied by fats and carbohydrates in amounts large enough to reduce protein metabolism to a minimum.

The optimum diet in nephrosis varies with individual requirements; that is, with the degree of albuminuria, presence or absence of infection, or of malnutrition, etc. Epstein advises the use of a diet containing 120–240 Gm. of protein but only 1280–2500 calories.⁶ More recently Liu and Chu,⁹ on the basis of nitrogen balance experiments on an adult with nephrosis, found 1.8 Gm. of protein and 60 calories per kilogram the optimum. For a child the needs for both were greater. In this clinic we have usually found diets containing from 90 to 125 Gm. protein and 2500 calories per day sufficient for an adult patient confined to bed. Rarely is anything to be gained by giving beyond 3000 calories per day, or 1.5 Gm. of protein per kilogram. In this regard our experience coincides more with that of Peters² and his co-workers than with Epstein or Liu.^{6, 9} It is well to use proteins of high biological value, and in our diets we use meat and casein liberally in all types of Bright's disease, animal and vegetable protein being used approximately in the ratio of two to one.

Salt restriction is imperative when the patient has edema. If he is given salt he will retain an isotonic equivalent of water, and store both as added edema fluid. Water restriction, on the other hand, is worse than useless in subjects with the nephrotic type of edema. If water, even in large volumes,

there is danger of a depletion of the sodium chloride supply of the body. Chloride may be lost by vomiting. Whereas in the normal man, the kidneys hold back chloride when the plasma chlorides fall below 96 millimols, the advanced nephritic no longer has this retaining ability.^{15, 16, 17} The two main salts in the body are sodium chloride and sodium bicarbonate. The inability of the kidney to hold back sodium chloride causes a loss of that if it is not given in the diet. The inability of the kidney to form ammonia causes a loss of the sodium bicarbonate. The result is a depletion of the total salt content of the body combined with more or less acidosis. With the salts an isotonic equivalent of water leaves the body. The result is dehydration. If salt restriction in this stage is practiced the patient may lose so much saline solution from his body that the desiccation itself is a threat to his life.

The kidney has lost its elasticity. It can neither hold back water and salt to prevent desiccation, nor can it excrete either water or salt at a more than moderate rate. The object of treatment with regard to these two substances is to administer both so that the amount which must be excreted is within the narrowed range of the kidney's action. Through most of the terminal stage (urea clearance below 20 per cent) 7 to 10 Gm. of sodium chloride² and 2 to 3 liters of fluids per day meet these requirements.

In patients bordering on uremic coma oliguria is frequently encountered. This oliguria may arise from either of two very different causes. In one, the functional excretory elements of the kidney have become so completely destroyed that only a small volume of fluid and a limited amount of salt per hour can pass through them. In such a case giving more fluid or salt merely results in unlimited retention. In such cases there is not enough functioning renal tissue left to maintain life and the condition is beyond treatment. Secondly, the oliguria may be due to desiccation of the body while the kidney still retains sufficient functional capacity to excrete a fair amount of fluids and solids, and to maintain life for an indefinite period if functional loss were not progressive. In such

as are necessary for any normal subjects. It has been observed by Linder, Lundsgaard and Van Slyke¹² that no appreciable hypoproteinemia develops unless the albuminuria is at least 1 Gm. per day.

Regarding dietary treatment in the terminal stage of hemorrhagic Bright's disease (we arbitrarily define this stage as occurring when the blood urea clearance in chronic cases falls permanently below 20 per cent of normal²⁰), there is by no means any unanimity of opinion. McCann⁴ is inclined to limit proteins to some degree. It has been our experience, however, as well as that of Addis³ and Peters² that forced limitation of either the amount or type of protein ingested is of no value and if carried to extremes can do harm. At this stage we do not force protein. As a rule it is wise to allow the patients to eat what they like, providing their choice is such that nutrition and nitrogen equilibrium are maintained. The anorexia and digestive disturbances accompanying the terminal stage usually serve as enough of a safeguard against excessive protein intake. Though by greatly restricting the protein intake it is possible to lower the blood urea and blood nonprotein nitrogen appreciably, it has been shown by Van Slyke, McIntosh, Möller, Hannon and Johnston,¹³ and by Cope,¹⁴ that the kidney function is not altered by this procedure, and we have not observed clinical improvement or any beneficial effect on the course of the disease by such restriction even though the blood urea has fallen markedly. On the other hand, we have frequently found it possible to keep a patient singularly free from symptoms and able to carry on practically normal activities, even to the very verge of uremic coma, when close attention has been paid to his general nutrition. The second case presented shows such circumstances.

We believe from our results that the most important goal of dietary therapy should be to maintain nutrition and nitrogen equilibrium. Failure to accomplish this may at this stage lead to loss of strength and consequently to a premature physical breakdown.

In the terminal stage and especially as uremia approaches

there is danger of a depletion of the sodium chloride supply of the body. Chloride may be lost by vomiting. Whereas in the normal man, the kidneys hold back chloride when the plasma chlorides fall below 96 millimols, the advanced nephritic no longer has this retaining ability.^{15, 16, 17} The two main salts in the body are sodium chloride and sodium bicarbonate. The inability of the kidney to hold back sodium chloride causes a loss of that if it is not given in the diet. The inability of the kidney to form ammonia causes a loss of the sodium bicarbonate. The result is a depletion of the total salt content of the body combined with more or less acidosis. With the salts an isotonic equivalent of water leaves the body. The result is dehydration. If salt restriction in this stage is practiced the patient may lose so much saline solution from his body that the desiccation itself is a threat to his life.

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a case administration of salt and water, advisably accompanied by glucose and, if acidosis is present, bicarbonate, may restore good diuresis and bring a patient back from uremia to a mild degree of normal activity.

It has been our experience that the clinical differentiation of the two types of oliguria usually is impossible. It is therefore advisable to assume tentatively that the oliguria is due to desiccation and to attempt to reestablish a flow of urine by saline administration. In one patient, for example, who gave a history of hemorrhagic Bright's disease of from three to four years' duration and who on admission had persistent vomiting, drowsiness, marked dehydration, a blood urea nitrogen of 163 mg. per 100 cc., a urea clearance of only 9 per cent of normal, and who excreted only 170 cc. of urine in twelve hours, the administration of a few Gm. of salt and 3000 to 4000 cc. of fluid daily caused the drowsiness to clear up within a few hours. The vomiting and dehydration ended in a week's time. Within three weeks the urine output equalled the fluid intake, the blood urea nitrogen fell to 82 mg. per 100 cc., and the urea clearance rose to 17 per cent of normal. Since discharge a year ago this patient has been almost symptom-free, and he has been able to work and support his family, though the blood urea clearance has fallen to 11 per cent of normal. This fall in function is probably progressive and irreversible; but there remains for some time to come sufficient functioning kidney tissue to maintain life and activity under a proper régime.

Heart failure complicates the treatment, and may lead to a dilemma. Large amounts of fluid and salt are contraindicated by the presence of marked cardiac edema, but at the same time may be indicated by salt depletion in the blood and by dehydration of the nonedematous tissues. Under such circumstances it may be impossible to meet the situation adequately, even with the use of digitalis. One steers as best one can between Scylla and Charybdis.

In hypertensive and arteriosclerotic Bright's disease, we have found protein restriction of no value. Nor have we even observed a fall in blood pressure during the administration of

a low salt diet, wherein such factors as rest, relief from emotional disturbances, or spontaneous variations in blood pressure could be definitely excluded as the cause of the fall. It is possible that in some cases salt restriction may be of benefit. We must report our results with this treatment as entirely negative, however. The only dietary measure we have observed to be of value in giving prolonged symptomatic relief in hypertension has been the use of a reduction diet in obese subjects.

I wish to present three patients.

Case I.—This man (Fig. 225), aged forty-four, has hemorrhagic Bright's disease. His illness dates back four years and began with the extraction of an abscessed tooth. The patient felt chilly and went to bed for a few days. Two weeks later he developed edema, which spread very rapidly, so that in another two weeks he had general anasarca, and was bed ridden. Albuminuria, cylinduria and microscopical hematuria were found. About six weeks after the onset of his illness, he was admitted to a local hospital remaining there about two months. His kidney function was very low. It is reported that the phenolsuphonephthalein excretion was only 5 per cent in two hours. Therapy consisted of a low protein, low salt diet, drastic catharsis, digitalization, and blood transfusion. The patient lost 20 pounds from loss of water, but the edema had not completely disappeared when he was discharged. On returning home there occurred a gradual progressive reaccumulation of edema which reached such a degree that the patient again became bed ridden. Reaccumulation of fluid was only interrupted for a few days by rigorous catharsis from time to time. There also developed marked weakness. Thirteen months after the onset of his illness his home physician advised a higher protein diet. The patient gained in strength and some of the edema disappeared, but he was still confined to bed, and the outstanding findings on admission to this hospital, fourteen months after the onset, were anasarca and a fair degree of wasting. His blood urea clearance was only 20 per cent of normal and he was at first regarded as being in the terminal stage of hemorrhagic Bright's disease. Moderate anemia was present. A microscopical hematuria was found. The plasma proteins measured 4 per cent and were therefore below the 5 per cent edema level.¹⁵ He excreted a great deal of albumin in the urine (averaging about 15 Gm. per day). There was only slight increase in systolic blood pressure. No abnormal changes were noted in the eyegrounds. The rest of the patient's course is represented in Fig. 225. Only the salient points will be discussed.

The patient's symptomatic improvement dates from the increase of protein in his diet one month before admission. However, it is probable even during that month the protein diet was still inadequate, because on admission we found that the patient could tolerate only 40 Gm. per day. As rapidly as it could be accomplished (one month) his diet was increased to 80 Gm. of

a case administration of salt and water, advisably accompanied by glucose and, if acidosis is present, bicarbonate, may restore good diuresis and bring a patient back from uremia to a mild degree of normal activity.

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In hypertensive and arteriosclerotic Bright's disease, we have found protein restriction of no value. Nor have we even observed a fall in blood pressure during the administration of

ment on a more adequate diet. The blood urea clearance rose to 35 per cent of normal after five months when all dietary restrictions were removed, and to 45 per cent of normal in the thirty-two months that have elapsed since he first came to the hospital. He excretes only a small amount of albumin at present, can concentrate to 1.020, the hemoglobin is nearly normal, and hematuria has not recurred.

It is probable that the high protein diet in this case had no direct influence on the eventual course of the disease. On the other hand, it seems fair to assume that by improving the nutrition of the patient, that is by giving him a diet more adequate in protein and calories, his convalescence was shortened. It is still doubtful whether the patient will completely recover, but he is now in the latent stage, has no symptoms, and is able to carry on perfectly normal activities.

Case II.—This patient, a girl of fifteen, also has hemorrhagic Bright's disease (Fig. 226), but is presented to show quite a different set of circumstances. The patient entered the hospital in November, 1929, forty-seven months ago. The disease had an insidious onset with edema and probably gross hematuria, four months before admission. She was first seen by a physician in September who prescribed a diet which consisted only of milk, spinach, and water, and during this time there was a marked increase in edema. On admission to this hospital, the patient showed general anasarca and was completely bed ridden. Her kidney function was 30 per cent of normal, as measured by the blood urea clearance. She had no anemia, but there was marked hematuria. The normal person excretes less than 500,000 red blood cells in a twelve-hour period.¹⁰ She excreted over 150,000,000 red blood cells in this time. There was marked reduction in the plasma proteins and considerable albuminuria. Her course is represented by Fig. 226. The edema disappeared very quickly on a diet of 60 Gm. of protein and 2000 calories. This represented 1.5 Gm. of protein and 45 calories per kilogram of true body weight. Her first stay in the hospital lasted nine months, during which time her kidney function did not improve significantly, although her general nutrition improved, as evidenced by a gain of 4 Kg. in tissue weight after she had lost 10 Kg. due to loss of fluid. After seven and one-half months all dietary restrictions were stopped. She has eaten about 80 Gm. of protein and about 2500 calories since that time. Since her first discharge she has only returned to the hospital for check-up examinations. There has occurred a progressive fall in kidney function, the urea clearance now being only 5.6 per cent of normal. A progressive anemia has also developed and at times, accompanying upper respiratory infections, there has been an increase in hematuria. Albuminuria has persisted, but the plasma proteins have remained normal. She has had no edema, is able to carry on perfectly normal activities, and in spite of the increase in blood pressure, increase in the size of the heart, and beginning ocular fundus changes, she has no troublesome

protein and 2500 calories. This was equivalent to 1.6 Gm. of protein and 50 calories per kilo of edema-free body weight. There then occurred a rapid improvement, as evidenced by a rise in urea clearance and the concentrating ability of the kidneys, a rapid increase in plasma proteins and the subsidence

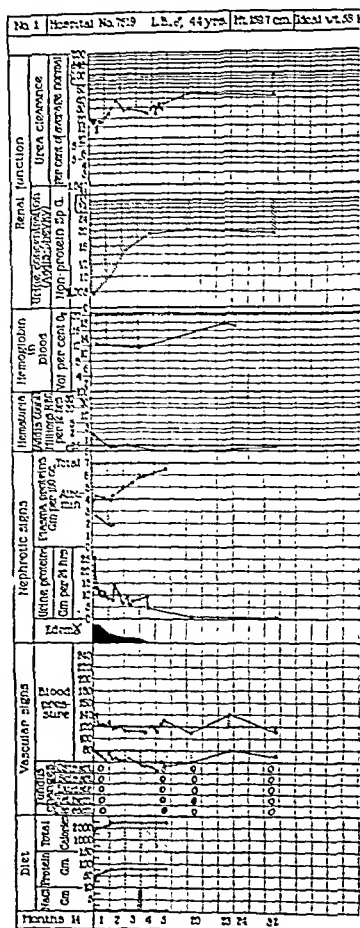


Fig. 225.

of hematuria. Decrease in albuminuria was much slower, however. The patient lost 21 kilograms, entirely from loss of water, and became edema-free in three and one-half months, at the same time his general nutrition improved. I think it fair to say that in this case a low protein diet delayed convalescence. This was evidenced by malnutrition on admission and the immediate improve-

vented invalidism due to edema and under-nutrition and has made it possible for the patient to carry on normal activities even up to the point where the inevitable breakdown due to the disease itself must occur. She is at present in an excellent state of nutrition.

I believe this case illustrates also how much we are in the dark regarding the cause of the symptoms of uremia. Cases such as this cast doubt on the logic of making the lowering of the blood urea a primary object in the dietary treatment in the terminal stages of Bright's disease. We are unaware of the factors which cause onset of uremic symptoms. Therefore, as borne out by this case, I think our attention in treating these patients may best be devoted to maintenance of adequate nutrition, rather than to attempts to lower the blood nonprotein nitrogen.

In the two cases just presented the regeneration of body protein on an adequate diet was very rapid. Such is not always the case, but it appears to occur oftener in patients that have previously been on a diet very low in protein and low in calories.

Case III.—The next patient, a girl, eighteen years of age, has degenerative Bright's disease (Fig. 227). She noted edema of insidious onset eleven months before admission to the Rockefeller Hospital. She was admitted to St. Luke's Hospital May 11, 1931, and transferred to the Rockefeller Hospital November 30, 1931. No permanent decrease in the amount of edema had occurred before she was transferred. We are indebted to St. Luke's Hospital for the following information regarding her diet.

May 12-14: Karell diet.

May 14-Aug. 24: C 150, F 30-40, P 100-120, salt-free, 1270-1440 cal.

Aug. 24-Sept. 15: C 125, F 100, P 30, salt-free, 1170 cal.

Sept. 25-29: C 130, F 40, P 120, salt-free, 1360 cal.

Sept. 30-Nov. 10: C 220, F 112, P 48, acid ash, salt-free, 2080 cal.

Nov. 11-30: Alkaline ash, calories 1800.

Although this patient was given a high protein diet by us (110 Gm. protein and 2200 calories, or 2.2 Gm. of protein and 46 calories per kilo of tissue per day) no improvement in the edema or rise in plasma proteins occurred for several months, and when improvement did occur it about coincided with the spontaneous and marked decrease in albuminuria. Following this improvement the kidney function rose, anemia decreased, and at present the patient is subjectively well, has a normal urea clearance, and no signs

symptoms. On admission her blood urea nitrogen was 25 mg. per 100 cc. In August, 1933, it was 109 mg. per 100 cc., and this represents 234 mg. urea per 100 cc. It is remarkable that the patient can reach such a low state of kidney function and yet be practically symptom free. The only symptoms elicited after persistent questioning are nocturia and occasional vomiting (after

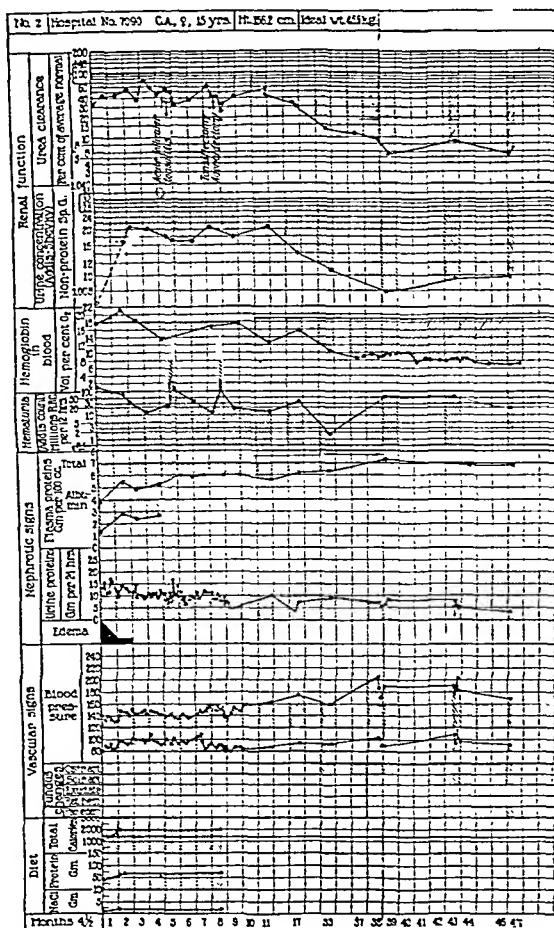


Fig. 226.

she has eaten food she does not like). The patient does not notice the anemia. Menstrual periods have been regular throughout her illness.

The adequate diet in this case probably has had no influence on the eventual course of the disease, but it has pre-

do not know. The fact that our knowledge is incomplete, however, does not justify creating an additional cause for lowering of the plasma proteins by the feeding of a low protein diet.

Summary.—We have discussed the conclusions reached in our clinic with regard to the feeding of protein, total calories, water, and salt in the different stages of Bright's disease. The general principle arrived at is that dietary treatment is most beneficial when it is aimed at maintenance of a good state of tissue nutrition and plasma protein content, and at maintenance of a normal supply of fluid in the body.

There is no evidence that low protein diets designed to rest the kidneys have any effect on the progress of the renal lesions. On the contrary, they are likely to cause unnecessary emaciation and weakness, and to favor the development of edema from plasma protein deficit. We therefore, in all stages of the disease, endeavor to maintain as nearly a normal state of blood and tissue nutrition as the patient's tolerance of protein and total calories will permit.

Salt restriction is required whenever there is a tendency for edema to accumulate. On the other hand, in the terminal stage of renal disease, when the kidneys largely lose their ability to restrict either chloride or water excretion according to internal need, it is desirable to administer salt and water in sufficient amounts to prevent desiccation.

Water restriction appears to have no justification in any stage of nephritis, unless cardiac failure is present.

EXPLANATION OF FIGURES 225, 226 AND 227

For renal function, hemoglobin in blood, hematuria, plasma proteins, and blood pressure the mean normal is drawn as a base line; the shaded areas between the base line and the point representing observations indicate the degree of deviation above or below the average normal. When the shaded area extends downward from the base line the observed value is below the normal average, and *vice versa*. Gross hematuria is plotted as columns extending above the 100 million mark.

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The brackets at the left of the scales for urea clearance, urine concentration and hematuria indicate the range of normal variability. The normal base line for hemoglobin values varies with the patient's age and sex.

The scales for urine protein and diet are obvious.

The black areas representing edema have the following significance.

Height of black area in quarters of total space.	Edema.
1	trace.
2	moderate pitting.
3	marked pitting.
4	general edema with ascites.

Under fundus changes we chart constriction of the arterioles, arteriolar sclerosis, exudate, retinal hemorrhages, and papilledema. In each instance shading by slanting lines mean minimal changes; cross hatching indicates moderate changes, while marked changes are shown by black areas.

The vertical spaces which are left unshaded indicate periods during which no observations were made, usually because the patient was out of the hospital.

At the bottom of each chart the number at the left nearest "months" indicates the number of months the disease was noted before the patient entered the hospital. The other numbers in the bottom row indicate months after first admission.

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to the yellowish pallor of the "chronic nephritic" as not unlike the pallor of the victim of pernicious anemia.

Cases.—We have as illustrative cases today, three patients with hypertension. Before they are sent into the amphitheatre, I should like to direct your attention to the *type* of disease they present.

The *first* patient has a blood count of 108 per cent hemoglobin and 6,190,000 red cells, *both* figures well *above* the average normal. You will note that he has the residual signs of a cerebral thrombosis or hemorrhage.

The *second* patient has a blood count of 76 per cent hemoglobin and 5,972,000 red cells; that is, the hemoglobin figure is reduced, but the erythrocyte count is normal or even slightly elevated. It will be observed that he is the victim of congestive cardiac failure. His anemia is reflected in the low hemoglobin value. This same anemia is "masked" (to use Dr. Ewing's excellent descriptive term) by the fact that the congestive heart failure, with its cyanosis and congestion of the fingertips and ears, "artificially" increases the red cell count.

The *third* patient has a blood count of 56 per cent hemoglobin and 3,616,000 red cells, *i. e.*, *both* the figures are markedly *below* normal. This patient has developed renal insufficiency.

When these patients have been presented, our discussion will be confined to this third type of case—that of impaired renal function and its accompanying anemia. You will thus observe that while the blood counts of patients with hypertension (either essential hypertension or elevated blood pressure associated with "nephritis") are normal throughout most of their course, there comes a time when they "express themselves" (if the term may be used) as cerebral, cardiac or renal cases, each with a distinctive type of blood count that gives a clue to the type of complication that has overtaken the patient.

Case I.—Mr. B., aged fifty-seven, retail storekeeper, came to the out-patient department for treatment of his blood pressure which he has known to be high for at least four years. In the past three or four months his

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ANEMIA IN BRIGHT'S DISEASE

Introduction.—For some years, at the New York Post-Graduate Medical School and Hospital, we have regarded the subject of what is commonly termed “nephritis” (but which should preferably be termed “Bright’s disease”) as a problem in which the analysis and the treatment are dependent upon six factors, as follows:

- I. The pathology of the kidney (*i. e.*, the nephritis), and of other tissues (*c. g.*, the eyegrounds).
- II. The renal function.
- III. The blood pressure (and cardiac complications).
- IV. Uremia.
- V. Edema.
- VI. Anemia.

The presence or absence of each of these factors, and the extent of its influence upon the composite clinical picture must be determined for each case as it presents itself, and treatment directed accordingly. The problem of anemia in Bright’s disease, the sixth of the above factors, has been assigned to me as my part of the present symposium.

A group of distinguished physicians have furnished description of the anemia that is encountered in the management of patients with Bright’s disease. Dieulafoy referred to “chloro-Brightismé.” Ewing’s text-book on blood diseases, published in 1903, discusses the subject in detail, ascribing importance to long-continued albuminuria and to parenchymatous changes in viscera as etiologic factors. Janeway spoke of the anemia as occurring especially in patients with Bright’s disease who also manifested achylia. Christian and O’Hare have referred

Symptoms.—We have, in the patient last presented, the usual clinical picture of anemia occurring in Bright's disease. The factor of anemia is often neglected both in treatment and in seeking a cause for the symptoms of the patient. It should be borne in mind that traces of albuminuria, dyspnea, anorexia, slight edema at the ankles, vertigo, weakness, apathy and even some diminution of the concentrating power of the kidney resulting in lowered specific gravity of the urine, may be the results not of the nephritis, uremia or hypertension, but solely if not in part, the effects of the anemia which coexists. Likewise, in seeking the etiology of otherwise unexplained anemia, a coexisting renal insufficiency should be suspected.

The blood count is usually of the "chlorotic" type with a low color index. However, in rare instances, the color index is over 1, and this, with the lemon-yellow pallor of the patient, may make the disease simulate true pernicious anemia. The degree of anemia is found to be proportional to the extent to which the renal function has been impaired and to the length of time that the renal insufficiency has existed. This is true of renal insufficiency whether due to primary or secondary contracted kidney, or to polycystic kidney or nephrolithiasis or any other cause. Thus, if the patient with nephritis manifests anemia although the kidney function is normal, some cause other than renal insufficiency should be sought as for example, a complicating mastoiditis in the nephritis associated with scarlet fever. On the other hand, if renal insufficiency of moderate or marked degree is present but there is no anemia, we may conclude that the impaired kidney function is of recent origin and that it has not yet existed long enough to yield the anemia which, in time, will be its invariable result.

Causes of the Anemia.—At least four factors, singly or in combination, may act to induce the anemia accompanying diminished kidney function. (1) Brown and Roth, who have pointed out that in chronic glomerular nephritis the degree of anemia parallels the blood creatinine retention, ascribe the blood deficiency to a *toxic effect* of the disease *upon the bone*

pressure has been read several times in the metabolism clinic and found to vary between 182/112 to 210/122. The blood count was 108 per cent hemoglobin and the red cells totalled 6,190,000, a distinct elevation of both figures. On another occasion, two weeks ago, the count was reported as 100 per cent hemoglobin with 5,940,000 red cells. This patient is shown briefly, to demonstrate the association of the "high" count with the evident cerebral vascular injury which he has suffered. This occurred about one year ago, being noted on awakening one morning. There are still the residual signs of weakness of the left cheek muscles, somewhat indistinct speech, weakness of right hand and arm and the slightly disturbed gait which was noted as he entered the room. Incidentally, his spleen is *not* enlarged.

Case II.—Mr. L., aged fifty, salesman, was told about eight years ago, on life insurance examination, that his blood pressure was "slightly more than normal." He was feeling perfectly well at the time. Two weeks ago he developed a nonproductive cough, had pain in the right upper and lower abdomen and within a day or two became moderately dyspneic and developed edema at the ankles. At present, physical examination shows an enlarged liver (to which may be ascribed the abdominal pain), moist râles at both bases, edema of the ankles and tibiae, dyspnea, cyanosis and auricular fibrillation with a pulse deficit. The liver was larger and the edema more pronounced four days ago when he was first seen and digitalis therapy instituted. The blood pressure is 188/124. The urine shows the usual evidences of chronic passive congestion of the kidneys which is borne out by a blood urea nitrogen of 32 mg. per 100 cc. The blood count is 76 per cent hemoglobin and 5,972,000 red cells—the hemoglobin reduced while the erythrocytes are above average normal.

Case III.—Mrs. C., aged forty-two, housewife, has had no known illnesses till one year ago when she had what was called "acute coryza and possibly sinusitis." Soon after her urine was examined and revealed marked amounts of albumin and a few casts. The urine since then has continued to show albumin and casts and its specific gravity has never been above 1.010 in the past four months. The blood pressure has varied between 178/110 to 196/116. There is some cardiac hypertrophy but there has never been cardiac decompensation. There is no edema. Her blood count is 56 per cent hemoglobin and 3,616,000 red cells—a secondary anemia, with both hemoglobin and erythrocytes markedly lowered. With this count we expect signs of renal insufficiency and they *do* exist. Examination reveals the "grapefruit" color of the skin, pallor of the mucous membranes and slight dyspnea. You have heard her complain of dizziness. The ankles and face are free of edema. The blood urea nitrogen is 56 mg. per 100 cc., the uric acid 4.05 mg. and the blood creatinine is 6 mg.

This is apparently a case of secondary contracted kidney. There must have been, at some time even before her "coryza" one year ago, an unrecognized acute nephritis—by no means a rare occurrence. The illness of one year ago merely provided a reason for examination of the urine and revealed evidences of *old* kidney damage.

measures allowing 60 or 80 Gm. of protein in the daily diet until the blood urea nitrogen reaches 40 or 50 mg. per 100 cc. If higher blood urea nitrogen figures result, the protein allowance is reduced either temporarily or permanently depending on the extent and duration of impairment of kidney function.

Use of Blood Transfusion.—Unfortunately, after an interval of months or years, the renal insufficiency of many of our patients with Bright's disease reaches such a degree of severity that their blood urea nitrogen is 40 or 60 mg. per 100 cc. even on diets extremely low in protein. The attempt to treat anemia by dietary measures must then be abandoned, but there remains another means at our disposal, the transfusion of blood.

We believe transfusions in Bright's disease are not performed as frequently as they might be. As was said at the beginning of our discussion of treatment, we must always bear in mind the objects of our procedures. We transfuse these patients to relieve their anemia and the symptoms due to their anemia. It is useless to undertake transfusion of blood as a "last resort" in uremia; nor does this measure apparently relieve edema. It will *not* elevate the blood pressure even in cases with marked hypertension as Dr. Mosenthal has shown repeatedly in numerous transfusions he has had carried out upon cases of marked hypertension and renal insufficiency. Of course, if the blood pressure is recorded while the patient is in bed in his room and is then read again after 100 cc. or more of blood have been introduced into his veins, an elevation of blood pressure may be observed in the second reading. But, if you will take the blood pressure repeatedly as the patient reaches the operating room you will note that the psychic effects of preparing for transfusion may have elevated the pressure to a point beyond which, however, it will *not* go, even if blood be introduced into the circulation. The body apparently has compensatory mechanisms whereby it prevents the rise of blood pressure that might be theoretically expected to result from increasing the blood volume. Anuria or hema-

marrow. (2) We have already mentioned the *parenchymatous changes in various viscera* (stomach, liver, intestines) referred to by Ewing and by Janeway as occurring in Bright's disease. (3) Another factor is the *limitation* which renal insufficiency imposes *upon the feeding of protein*. At some of the stages of these patients' illness, sufficient protein to avoid or correct anemia cannot be fed without markedly increasing the blood urea nitrogen. In fact, in some cases an insufficient protein intake, arbitrarily and unnecessarily imposed as soon as the patient becomes aware of an elevated blood pressure even if renal function is excellent, yields an anemia even in the absence of impaired kidney function. (4) The effect of long-continued *albuminuria* must be considered as a possible cause of anemia in some patients though in others, despite ten years or more of persistent albuminuria, no anemia supervenes.

Objects of Treatment.—How shall we treat the anemia? Or first, what is the importance of treating it? Obviously, if the anemia can be overcome many distressing effects of this blood deficiency will be relieved. Again, untreated anemia is itself a factor that will shorten the lives of these patients or reduce them to invalidism. Even if correction of the anemia produces no effects upon the course or duration of the Bright's disease, we have in the treatment of the anemia a means whereby the life allotted to the victim of progressive renal insufficiency is made comparatively comfortable, even enabling many of these patients to carry on considerable business and social activity. We must keep before us the idea that we are treating but one of the factors that make up the picture of Bright's disease. We must not expect to alter the renal pathology or to cure uremia or relieve edema by the treatment directed toward alleviation of the reduced blood count. But we *do* expect to relieve the debilitating effects of the anemia.

Treatment.—Any preventive measures (as avoidance of colds and exanthemata or removal of foci of infection) which prevent renal insufficiency, will prevent the resulting anemia. When the anemia is encountered, we treat it first by dietary

turia or other ill-effects of transfusion do not occur if the blood-grouping has been accurate and if macroscopical as well as microscopical cross-agglutination is carried out before each transfusion even if the same donor is used. It is not enough merely to take donors of the same blood group as the recipient or to assume that if the blood of a particular donor has not agglutinated the patient's blood at one time that it will not do so at another. In short, with properly "matched" blood we see no contraindication to transfusion in Bright's disease, but we stress the fact that the object is to relieve anemia, not to perform miracles upon moribund patients.

A single transfusion while helping the patient, will not reflect any improvement in the blood count nor relieve him completely. Our procedure has been to give a transfusion of 500 cc. to 1000 cc. of blood, repeat in five to seven days and finally give a third transfusion after a similar interval. When such a routine has been carried out the patient's improved blood count remains at a normal level for intervals of three or six months to a year before further transfusion is necessary depending upon how late or early in the course of his renal insufficiency we have put him under this treatment.

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I have written upon the blackboard a list of references for any of you who might wish to investigate this subject in greater detail.

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due to racial characteristics, environmental conditions, dietary, hygienic, social, and economic factors. It would be better to compare each individual child with an "ideal" status rather than an "average" status, determined by clinical impression—the relation of flesh to skeletal growth, a fulness of development—tonus—vitality. This clinical impression should be checked by some concrete measurement of nutritional status, which is rather individual than average. Such a measurement we have in the "Pelidisi Index" of Pirquet.¹ By means of the pelidisi we can judge whether the actual weight of the child corresponds to the ideal weight of a child with a given sitting height. The sitting height is perhaps not an exact measure, as no measure which is not applied exclusively to a rigid bone but also includes joints, can be considered as mathematically exact. However, the sitting height shows smaller individual variations as the child increases in size than does the total height, and it bears a close relation to the body weight throughout life. This relation may be expressed as $Si^3 = 10 \times \text{weight in grams}$, and therefore $\sqrt[3]{10 \text{ wt.}}$ equals sitting height; or $\frac{\sqrt[3]{10 \text{ wt.}}}{Si} = 1$.

If the weight is more than usual, the relation will be less than 1; if the weight is less than usual, the relation will be more than 1. In adults a greater proportion of musculature raises the index about 5 points, so that thin people are those with a pelidisi under 95, fat people over 105. In children where the musculature is not so well developed, the thin child is the one with a pelidisi index under 90, the fat child will reach above the 100 mark. Marked deviations from the expected pelidisi may be considered abnormal nutritional states.

UNDERNUTRITION

Failure to gain properly is very common among children, and such cases occupy a large part of the time and attention of the practitioner. Many degrees of undernutrition exist and the underlying causes are various.

A small proportion of such children are delicate from birth due to inherited constitutional inferiority. They may be the

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ABNORMAL NUTRITIONAL STATES IN CHILDREN

THE subject first assigned for this lecture was "marasmus in infancy." Fortunately marasmus in infants in the old sense no longer exists in this country. The elimination of this deplorable condition is due to two factors: (1) The better milk supply, as a result of a system of inspection of dairies, creameries, and pasteurizing plants; and of the improved methods of shipment and handling all the way from farmer to consumer. (2) Education of the lay public by means of pamphlets published by the United States Government, radio talks, baby health stations, nurseries and clinics in connection with nearly all hospitals.

The intention is therefore to widen the scope of this lecture to include abnormal nutritional states—both overnutrition and undernutrition—especially in children beyond infancy.

What constitutes an abnormal nutritional state? The normality of nutrition may be judged by:

1. Relationship between weight, height and age.
2. Anthropometric measurements indicating growth.
3. Clinical appearance.

Hard and fast lines do not exist. Ocular impressions are valuable, substantiated by careful physical examination and comparison with some recognized standards. Personal impressions are of great value in estimating the state of normality, and a physician instinctively judges whether a child appears well nourished or undernourished. Our conception of normality has necessarily been based to a great extent on a large number of measurements of children of varying ages, weights, and heights, and this indicates average growth of the child. We call this normal. Differences in normal may be

disturbed. The appetite is poor. Mentally these children are often bright, even precocious.

As the child grows older, the problem may become simpler, as he may outgrow bad habits of feeding, and the chances of his eating more normally and growing stronger each year are better. If the condition, however, is influenced by constitutional factors, it is likely to last throughout the first part of childhood, but often spontaneously improves around the time of puberty, at which time there may be a tendency to an increase in weight and height, as a result of the tremendous growth stimulus at this period.

OVERNUTRITION

The condition of overnutrition is very common in adults—less so in children, although prevalent to a certain extent. The lay public is tremendously interested in the subject of obesity; but unfortunately this large amount of interest is in inverse proportion to the small amount of scientific knowledge on the subject. Although normally there is a fairly accurate adjustment between caloric intake and energy output, we still do not know why certain people get fat, even with a conscious limitation of their dietaries; while others maintain a constant weight without the use of scales or strict diets. The whole subject is still full of unsolved problems. Authors vary in their opinions as to the cause of obesity, from those who believe that there is an endocrine disturbance in all cases, to those who believe that all obesity is a result of overfeeding.

Theoretically the division into the various forms of obesity is as follows:

1. Exogenous obesity, due to overfeeding or underactivity, or both.

2. Endogenous obesity of

- (a) Frank glandular etiology such as:

1. Myxedema due to hypothyroid function;
 2. Obesity of the gonadal type such as that following castration;
 3. Obesity associated with pituitary dysfunction; *c. g.*, the Fröhlich type.

offspring of parents of poor physical development, or afflicted with tuberculosis or syphilis. Among the poor, the condition may be exaggerated by poor hygiene, insufficient or improper feeding, overcrowding, etc. Among the well-to-do, it may be seen in the spoiled child, or the child of high-strung nervous parents. These children are often intelligent, sweet and playful, but are stubborn tyrants when it comes to eating their meals. They torture their mothers or nurses at the feeding table.

Many cases of undernutrition are traceable to digestive disturbances with frequent relapses dating far back to infancy or the second year of life.

It is self-evident that different kinds of chronic infection, especially tubercular infection, but also infections of the nasopharynx and of the respiratory tract, may be responsible for lack of appetite and refusal of sufficient intake of food with resulting undernutrition. Sometimes the seat of infection may be obscure, and fever need not necessarily be present to indicate the presence of the infection.

Later in childhood, overpressure in school, or overstimulation as a result of too many extra-school activities may have a deleterious effect on the nutritional state by affecting the appetite. Emotional upheavals due to unpleasantness in school may work in the same direction. The morning rush to school in the dread of being "late" frequently interferes with taking sufficient food at breakfast time; or having bolted food under compulsion, vomiting occurs, and the end-result is insufficient intake of food. Characteristically, these children never vomit on school-free days.

It may be pointed out that the situation is less serious if only the weight and not the growth has suffered. The general physical development may be below normal. The muscular development may be retarded, the muscles lacking tonus. Such children often tire easily. Their circulation may be sluggish. Attacks of acute indigestion may be brought about by overfeeding—an error which is often made by the overanxious mother in an attempt to fatten the child. Sleep is often easily

During periods of decreased appetite, the fat reserves are drawn upon.

THE BASAL METABOLISM

The basal metabolism in normal children varies with age, sex, and size, and in childhood, especially, is influenced by growth, puberty, and nutritional states. At birth the basal metabolism is very low. It increases rapidly during the first year of life, as the muscles begin to acquire tonus, as the central nervous system develops, and as the endocrine glands begin to function. After the first year, there is a steady rise

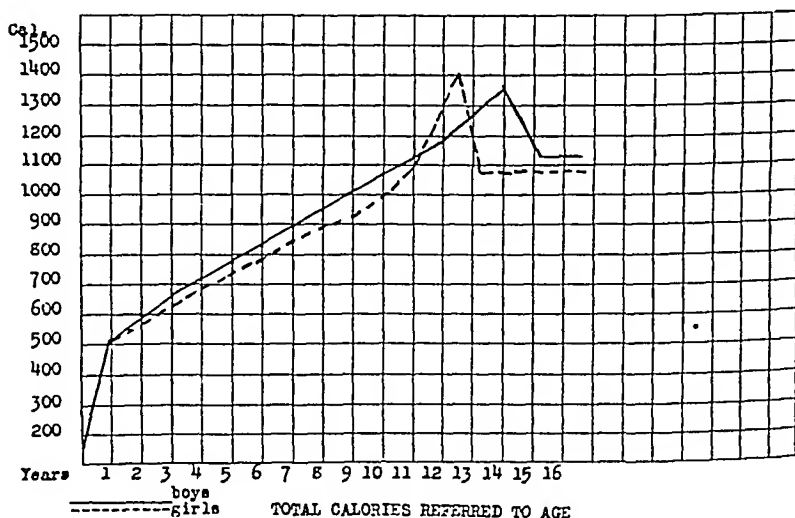


Fig. 228.—Basal metabolism of normal children. Note increase during puberty.

in metabolism, until early puberty, when there is a very rapid increase, occurring somewhat earlier in girls than in boys, associated with their earlier maturity (Fig. 228). It may theoretically be said that during the first year of life, a condition of physiologic hypothyroidism exists—the “pig” stage of childhood—at which time the infant is easy to fatten. In contrast to this, the period of puberty is a period of physiologic hyperthyroidism, during which time the endocrine glands are functioning intensively, the sex life begins to awaken, and there are many and profound psychic and physiologic

- (b) Constitutional obesity, due neither to overfeeding or laziness, nor yet to an endocrine disturbance; but caused by a constitutional tendency to obesity, which explanation of course does not explain the situation.

Perhaps an endocrine factor enters into all types of obesity in rapidly growing children, as this factor influences temperament, psyche, the desire for food, the desire for activity, etc.

NORMAL NUTRITION

The maintenance of a normal state of nutrition depends on the total daily metabolism which may be said to have four components:

1. *The Basal Metabolism*.—By this term is meant the heat production when the body is at complete rest, and at a sufficient interval after a meal to escape the stimulating effect of food. Such heat is produced as a by-product of chemical action in living cells—skeletal muscles, the vital organs, glands, etc.

2. The additional energy necessary for the *muscular work* of the day. Naturally this depends on the kind and amount of activity. In children, the heat output of the energy expended in play must be provided for.

3. The surplus energy required for the ingestion of food—known as the *specific dynamic action* of food. This stimulus is greatest for protein, and least for fat.

4. The additional energy needed in childhood for *growth and development*, increase in length, growth of internal organs, increase in muscular and fatty tissue.

The addition of these four factors gives the total sum of the daily metabolic needs of the child. In the normal individual, the whole metabolism keeps its balance only when the total calories taken during the day equals the total daily metabolic needs. In the event that less is taken, there will be a negative balance of energy with loss of body weight. If an excess is taken, that excess is stored as body fat. Usually the adjustment of expenditure and intake is regulated by appetite.

ally diminish. On such a régime, reductions in metabolism as much as 20 per cent have been produced. The muscular development of the underfed child is retarded, and there is also a loss of muscle tone. Perhaps these factors also contribute to the lowering of the basal metabolism in undernutrition.

In obesity, unless definitely of endocrine origin, there is no abnormality of metabolism demonstrable by our present methods. The tendency is however toward a high normal rate (Fig. 230). This is especially true of obesity due to overfeeding. Obesity may be considered as a condition of overnutrition of the body cells. This condition of cell plethora accounts for the increased oxidations. Helmreich and Wagner⁴

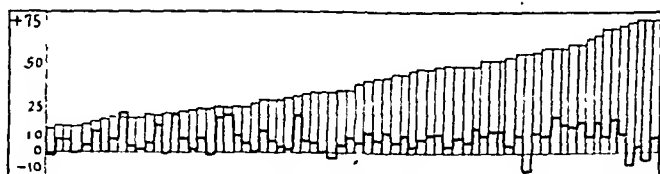


Fig. 230.—Basal metabolism of overweight children: Upper curve shows individual percentage of deviation from normal weight; lower curve shows corresponding individual percentage of deviation from normal basal metabolism. Note that the majority of the basal metabolism readings are "plus" figures and above the zero line. (From Topper and Mulier in *Jour. Amer. Med. Assoc.*, vol. 92, p. 1903, June 8, 1929.)

studied nine children, first on a maintenance diet, then on an increased diet. They found that after a period of overnutrition, the basal metabolism increased from 6 to 18 per cent when the extra calories were in the form of sugar or fat; from 14 to 25 per cent when the extra calories were in the form of protein. The level of the basal metabolism is evidently not an absolute one, but depends rather on the nutritional condition of the cells.

METABOLISM OF MUSCULAR ACTIVITY

Lavoisier's discovery in 1780 that the absorption of oxygen is increased during mechanical work firmly established the fact that physical activity stimulates the cells to increased chemical activity, with an increased heat production. This in-

changes. There may also be other symptoms of hyperthyroidism at this time, nervousness, tremor, vasomotor instability, tachycardia, functional murmurs, etc.—all evidence of greatly increased chemical activity. During this period of early puberty, nutritional care is important from the point of view of preventing certain diseases which attack the undernourished child.

In undernutrition, the basal metabolism, while it may remain normal, is usually lowered (Fig. 229). Evidently undernutrition acts as a depressant to the basal metabolism—perhaps

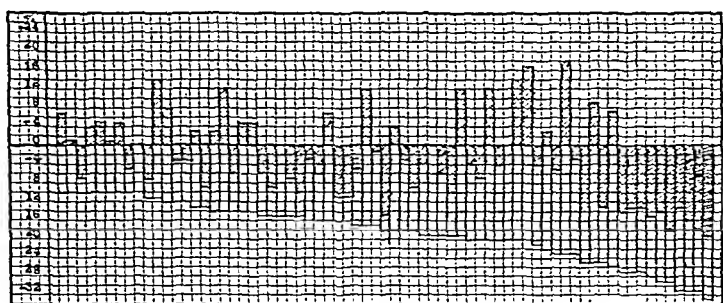


Fig. 229.—Basal metabolism of underweight children; upper curve (shaded part) shows the percentage of deviation from the normal basal metabolism of each child; lower curve (unshaded part) shows, correspondingly, the percentage of deviation from the normal weight of each child. The majority of the basal metabolism readings are “minus” figures and below the zero line. This shows that the nutritional state of the child is one of the determining factors for the level of the basal metabolic rate. (Topper and Mulier in Amer. Jour. Diseases of Child., vol. 38, p. 299, 1929.)

a compensatory economy of oxidations which tends to protect the organism from the evil results of starvation. There seems to be a gradual adaptation downward of the metabolism to a long-continued decreased intake of food. In severe malnutrition, the metabolism may drop to 30 per cent or more below the normal level. There is some evidence that the reduction in metabolism is due less to the lowered caloric intake than it is to the low protein content of the diet. Krogh² and later Duell³ showed that if an individual is given a diet high in calories but low in protein, his basal metabolism will gradu-

action of food, while in undernutrition there may be an increase in this cost of digestion, especially in the nervous type of child. Although this factor may not in itself play a sufficient rôle to account for the retention of the abnormal nutritional state, it may help us in treating the condition.

NEGATIVE PHASE

Bernhardt has made some interesting studies which may throw a little light on the etiology of obesity. He studied the daily metabolism of obese and of normal individuals. He found that there was a negative phase in the metabolism—that the metabolism fell below the basal rate during sleep, and after the disappearance of the stimulating effect of food and muscular activity. This negative phase lasted longer in obese than in normal individuals. He believes that the sum of these negative phases lowers the total daily metabolic needs of obese individuals, so that what we consider a basal diet for these obese people is really enough to make them put on additional weight.

FACTOR OF SATIETY

Another interesting theory which may explain obesity and undernutrition in part was advanced by Strand and MacClugage.⁹ They believe that abnormal nutritional states depend on a feeling of satiety rather than on differences in effect of work or of food. In normal people, the peak of satiety after eating corresponds with the peak of the specific dynamic action. In the undernourished, the peak of satiety is reached long before the peak of the specific dynamic action of the meal; while obese individuals fail to reach the peak of satiety. They conclude that the thin person stays thin because at his low metabolic level, fewer calories suffice to give the "optimum sensation of comfort," while the obese person at his higher metabolic plane requires 3000 or more calories to reach this same optimum sensation.

TREATMENT OF ABNORMAL NUTRITIONAL STATES

All these principles may be applied in the treatment of abnormal nutritional states.

crease in metabolism is temporary. But continued activity raises, in addition, the plane of the metabolism. The metabolism of laborers, or of athletes, for example is higher than the metabolism of nonathletic individuals, or of those who lead a sedentary life.

Convincing studies on the muscular efficiency of obesity seem to be lacking. Gessler⁵ (Heidelberg) found that obese people doing the same muscular work as normal people showed an increased metabolism which was however 20 per cent lower than the increase of the normal people. This might be an important factor in the maintenance of obesity; but unfortunately other investigators could not confirm these results. Lauter⁶ found a higher increase of the basal metabolism of obese children due to activity. Bernhardt⁷ (Berlin) found the same increase after light muscular work in obese and in normals; while after severe muscular work, there was a greater increase in the metabolism of the obese. Lauter believes that in obesity it is not the efficiency that is lacking but rather the impulse to movement because movement is accomplished at a greater expense than normally.

As to muscular efficiency and heat production in undernutrition, Benedict⁸ observed a squad of college students while rapidly losing weight. He found no alteration in their muscular efficiency. But there was a feeling of general weakness and tiredness, so that in order to work, these boys had to drive themselves. Undernourished children conserve their energy for growth and will automatically cut down on their activity; or in the excitement of competition they may be led to excessive exercise and thus to a lack of gain in weight.

Both in overnourished and in undernourished children, there seems to be a normal increase in metabolism due to activity—but there may be a difference in that the impulse to movement is lacking.

SPECIFIC DYNAMIC ACTION OF FOOD

Most investigators agree that in obesity, especially of the pituitary type, there is a reduction in the specific dynamic

favorable conditions for the normal development of the growing body.

The basal metabolism may be kept on a high normal plane in several ways: (a) by a high protein content in the diet.

It is well known that feeding a high protein diet will keep the basal metabolism on a high plane. Lusk¹² found that when a large quantity of protein is ingested day after day, the usual specific dynamic action of the protein occurs, and also a continued "secondary" rise in the total day-to-day metabolism. Therefore in planning a reduction diet, a high percentage of protein may be allowed in order to offset the reduction of the metabolic plane caused by the lowered caloric intake. A high protein content will also spare body protein, and will maintain the normal rate of growth in children. In a basal diet, the protein content may be as high as 40 to 50 per cent as the total amount of protein even then will be little more than the normal protein content of a normal child's maintenance diet.

(b) By increased muscular activity, which will stimulate the metabolism, not only temporarily, but according to Benedict and Smith,¹³ will effect a permanent increase in the level of the total metabolism.

(c) By thyroid administration, especially in those cases where the basal metabolism is low. It should be remembered, however, that normal children with a normal basal metabolic rate may fail to react metabolically to amounts of thyroid which are invariably effective in cretinism and myxedema. The stimulating effect of externally administered thyroid evidently varies with the amount of intrinsic secretion in the organism; the lower the amount of thyroxine in the tissues, the easier does such an individual respond to externally administered thyroid substances; the more normal the state of thyroxine in the tissues, the more resistant is such a child to the thyroid action. When thyroid extracts are administered with a view to raising the level of the metabolic rate, their action must be checked by metabolism tests. However, even where the metabolic effect is lacking, thyroid substance will

Treatment of Overnutrition.—In planning a diet for loss of weight in children, certain principles should be observed:

1. The total caloric intake should be lowered to the basal requirements calculated from the actual basal metabolic rate. The apparatus for testing the basal metabolism is now very simple and available in every clinic and hospital, and indeed in almost every physician's office.

Where the apparatus is not available, the basal metabolism may be roughly approximated from the Read¹⁰ Pulse Rate-Pulse Pressure Formula, which reads as follows: $0.75 \times \text{pulse rate per minute} + 0.74 \times \text{pulse pressure (difference between systolic and diastolic readings)} - 72$, equals the basal metabolic rate per cent. Pulse rate and pressure must be taken under the same conditions as the basal metabolism, *i. e.*, in the postabsorptive state and with the patient lying down and at rest for thirty minutes. Read and others have found that under these conditions the pulse rate-pressure complex is a fairly accurate prediction of the basal metabolic rate, and in normal individuals, gives readings within 20 per cent in about 80 per cent of cases. While this is not accurate enough for scientific work, it at least gives a working idea of what the basal requirements may be.

By a reduction of the total caloric intake to the body's basal needs, the organism is compelled to use up its own fat and glycogen reserves for any additional energy requirements for the day.

2. Lowering the total caloric intake will result in lowering the basal metabolism. As the level of the metabolism becomes lower, a diet which was previously enough to cause a loss of weight, at the new basal level, may be sufficient to cause a stationary weight curve, or even a gain; hence the level of the metabolism must be kept high. Helmreich¹¹ observed that the basal metabolism increased gradually after a child's diet was increased to double the amount; so that after two or three weeks of increased caloric intake, the level increased 20 per cent. After the diet was diminished to the previous amount, the basal metabolism gradually decreased, and after fourteen days reached the primary level. In reducing the weight of children, one must aim therefore to keep the basal metabolic rate on a normal level. It is not sufficient only to increase oxidations in the body, but one must create

40 per cent carbohydrate and 20 per cent fat. In addition it contains bulky foods for satiety, and the fluid content is limited. The vitamin and mineral requirements have been met. In addition a list of foods, approximating 100-calorie portions, is given, which may be added to the basic diet as required. These foods have been chosen with an eye to a high protein content. The amount of calories given to the obese child should equal his determined or approximated basal metabolic rate.

The problem of overfeeding in childhood is very important. Czerny believes that overfeeding is responsible for lowered resistance to infection, resulting in higher mortality among these children. He believes that their impaired vitality increases postoperative risk among the obese. Overfeeding leads to gastric and intestinal disturbances, to abnormal water retention, lymphatic hyperplasia, and premature sexual development. Czerny finds that overfeeding of children with exudative diathesis often provokes eruptions of skin and mucous membranes, attacks of bronchial asthma, etc. Joslin¹⁶ emphasizes the correlation of obesity with diabetes. He believes that the overweight person is at least twice, and at some ages, forty times as liable to develop diabetes, as is the normal person.

The obese child often develops a sense of inferiority due to an inability to compete with his schoolmates in athletic activities and to the undue attention which he attracts.

When one knows the dangers that may result from excessive obesity, one realizes that prophylaxis in combating the evil results of overfeeding is of great importance in childhood. It should be the duty of every physician to warn parents of the undesirable consequences that may ensue if such a tendency is not controlled.

Treatment of Undernutrition.—In planning a diet for the increase of weight, the following principles should be observed:

1. A high caloric intake, sufficient to cover the basal requirements, plus 10 to 15 per cent for the specific dynamic action of food, plus sufficient for the daily energy requirements

increase the excretion of water and salts—which brings us to the third principle of a reducing diet.

3. Limitation of salt and water intake. Water and salt retention may account for failure to reduce some persons on the ordinary reduction diets. Studies of the Volhard water test and of the McClure-Aldrich intradermal salt solution test showed a definite diminution of urinary output and a rapid salt absorption.¹⁴ On a restricted salt diet and dehydration régime, these patients lost weight rapidly. Thyroid may be used for its diuretic effect in these obese children.

Recently dinitrophenol has been used to raise the basal metabolic rate in cases of obesity, where low caloric diets and thyroid have been insufficient to cause loss of weight.¹⁵ As the dosage has not as yet been established, and as toxic reactions occur—even to fatal pyrexia—the drug should not be used in children at present.

Chart 1 shows the sort of basic reducing diet used at our obesity clinic. This diet contains about 40 per cent protein,

CHART 1
BASIC DIET FOR OBESITY

		Grams			Calo- ries. 1000
Gm.	Approximate amount.	Coh. 100	Pro. 95	Fat. 25	
BREAKFAST					
100 10% Fruit	1 medium orange	10	1		44
2 Eggs			14	10	146
10 Bread	1 thin slice	10.6	1.8	.2	51
30 Pot cheese	1 ounce	1.2	6.3	.3	33
100 Skim milk	$\frac{1}{2}$ glass	5	3		32
		26.8	26.1	10.5	304
DINNER					
120 Meat, lean	4 ounces		24	6	150
100 4% Vegetable	$\frac{1}{2}$ cup spinach	4	1		20
100 4% Vegetable	1 medium lettuce salad	4	1		20
100 10% Fruit	$\frac{1}{2}$ grapefruit	10	1		44
20 Bread	1 thin slice	10.6	1.8	.2	51
		28.6	28.8	6.2	285
3 P. M.					
1 Cracker		5.1	.7	.6	29
45 Pot cheese	1 $\frac{1}{2}$ ounces	1.8	9.5	.5	50
100 4% Vegetable	1 medium tomato	4	1		20
		10.9	11.2	1.1	99
SUPPER					
1 Egg			7	5	73
90 Pot cheese	3 ounces	3.6	18.9	.9	98
100 4% Vegetable	1 cup cabbage	4	1		20
100 15% Fruit	1 medium apple	15	1		64
20 Bread	1 thin slice	10.6	1.8	.2	51
		33.2	29.7	6.1	306
Total		99.5	95.8	23.9	996

and lost in the urine and feces—and causes unnecessary increase in the basal metabolic plane.

(b) Sufficient rest. In those cases which are most resistant, sometimes spending the morning hours, or at least several hours a day in bed, with decrease in physical activity, will often accomplish the desired gain in weight.

(c) In certain cases of hyperactive children, who are restless at night, irritable, and fidgety, luminal in small doses will effect a decreased irritability of cells with a lowered basal metabolism.

3. The use of insulin to stimulate the appetite has become known within the past ten years and has been used especially for adults in European clinics and only recently for children in American clinics. The dosage given is anywhere from 3 to 10 units two or three times daily, twenty minutes before meals. It has been found that regardless of age, children who receive insulin eat half as much again as the amount they ate before they received the insulin, with a resulting gain of $\frac{1}{2}$ to $2\frac{1}{2}$ pounds weekly. The dangers of course are those of insulin shock, with symptoms of hypoglycemia, and therefore hospitalization is advised in cases where this treatment is to be used. The purpose of such treatment is to establish better habits of eating.

PSYCHOLOGICAL FACTOR

The psychological aspect of undernutrition must be considered. Sufficient calories to meet the energy requirements of the child will always result in a gain in weight—there is no miracle in maintaining the proper weight; but there may be a psychological background to the lack of desire for food. An overanxious mother, an atmosphere of hysteria, a child who subconsciously makes a bid for the center of the stage by his caprices, or by trying to demonstrate his will power—these factors may be at the bottom of an undernutritional state. Such children, when placed in a new environment, will eat everything set before them. For example, most children at the hospital eat all that is given them. The heartiest eaters at the

ABNORMAL NUTRITIONAL STATES IN CHILDREN

of the child. The proper estimation of the heat output of actively growing children can probably never be accurately calculated—they can only be guessed at. Many hours of the day are spent in the schoolroom. Benedict's estimate of the approximate allowance for school activities would be 10 per cent above the basal for active boys, and 20 per cent for girls. Time spent in the schoolroom is usually from six to six hours of the day; the basal requirements are approximately those during sleep—eight to twelve hours—counts for sixteen to eighteen of the twenty-four hours. During the remaining six hours, the child may be occupied in various kinds of physical activity, during which the heat output is highly speculative. It is well to allow anywhere from 10 to 20 per cent above the basal requirements depending on the degree of activity of the undernourished child. Aside from the possibility of digestive upsets, it is perhaps impossible to supply such a child with an excessive amount of food. Every effort should be made to secure a maximum growth and an ideal pelidisi. As many of these undernourished children are at the same time a small appetite, the diet should be concentrated—not bulky—so that a maximal nutritional result results from a minimal amount or volume of food.

2. As the caloric intake is increased, the basal metabolism will also increase, so that what was at first sufficient to cause a gain in weight will finally be insufficient. This is analogous to the feeding of pigs or geese, which are being fattened for market. As the diet is increased, the metabolism also increases, so that in order to effect a weight gain at the new plane of metabolism, the diet will have to be still further increased, and this goes on until the farmer finds it too expensive to further fatten the animals, and therefore sells them.

The total plane of metabolism should be kept at a low level. This may be done by: (a) a low protein diet. A minimum amount of protein should be given. This is usually calculated at about 10 to 15 per cent. This is the minimum required for growth and for digestion. Anything more than this is wasteful—about 20 per cent of protein being unoxidized

CHART 3

SUPPLEMENTARY FOODS TO BE USED WITH BASIC DIETS

4% Vegetables:

Asparagus
Celery
Rhubarb
Spinach
Cabbage
Cauliflower
String beans

8% Vegetables:

Beets
Green peas (canned)
Turnips
Squash

10% Fruits:

Substitute for 1 medium orange: $\frac{1}{2}$ grapefruit
1 slice pineapple
1 medium peach
1 small dish muskmelon or watermelon
 $\frac{3}{4}$ cup strawberries

15% Fruits:

Substitute for apple: 2 apricots
25 cherries
1 small pear
 $\frac{3}{4}$ cup huckleberries or blueberries
 $\frac{1}{2}$ cup raspberries
 $\frac{1}{2}$ medium banana

100 (approximate) calorie portions foods to be added to basic obesity diet:

15 Bacon	2 slices
90 Chicken	3 ounces
60 Meat (lean)	2 ounces
75 Liver	2 $\frac{1}{2}$ ounces
75 Fish	2 $\frac{1}{2}$ ounces
25 American cheese	2 thin slices
90 Pot cheese	3 ounces
30 Cream cheese	1 ounce
300 Skim milk	1 $\frac{1}{2}$ glasses
150 Buttermilk	$\frac{3}{4}$ glass
1 $\frac{1}{2}$ Eggs	

100 calorie portions foods to be added to basic undernutrition diet:

100 Potato	1 small
100 Corn	$\frac{1}{2}$ cup
50 Sweet potato	2 ounces
150 15% Fruit	
40 Bread	2 thin slices
8 Saltines	
3 Crackers	
150 Macaroni	1 cup (cooked)
50 Light cream	$\frac{1}{2}$ cup
25 Heavy cream	2 tablespoons
60 Evaporated milk	2 ounces
50 Ice cream	2 level tablespoons
20 Chocolate (sweet)	$\frac{1}{2}$ ounce
20 Peanuts	

hospital may be the very children who are the most difficult to feed at home. Early education in a taste for different foods is essential because at an early age, the child has not yet been conditioned by his environment to assert his will power and desire.

CHART 2
BASIC DIET FOR MALNUTRITION

		Gm.			Calo- ries. 1400
Gm.	Approximate amount.	Coh. 185	Pro. 40	Fat. 55	
BREAKFAST					
150 Milk	$\frac{3}{4}$ glass	7.5	4.5	6	102
10 Sugar	2 teaspoons	10			40
10 Farina	2 teaspoons	8	1		36
5 Butter	$\frac{1}{2}$ square			4.3	39
15 20°C Cream	$\frac{1}{2}$ ounce	.8	.5	2.9	31
20 Bread	1 thin slice	10.6	1.8	.2	51
5 Butter	$\frac{1}{2}$ square			4.3	39
100 Milk	$\frac{1}{2}$ glass	5	3	4	68
		41.9	10.8	21.7	406
DINNER					
30 Meat	1 ounce		6	3.6	56
50 Potato	$\frac{1}{2}$ small	10	1.5		46
5 Butter	$\frac{1}{2}$ square			4.3	39
50 Vegetable	$\frac{1}{3}$ cup	4	.5		18
5 Butter	$\frac{1}{2}$ square			4.3	39
Pudding or cake	1 small piece	30	3	8	204
		44	11	20.2	402
3 P. M.					
150 Banana	1 large	30	1.5		126
or substitute 15% fruit					
SUPPER					
1 Egg			7	5	73
20 Bread	1 thin slice	10.6	1.8	.2	51
15 Cream cheese	$\frac{1}{2}$ ounce	.2	2.9	4.1	49
5 Jam	1 teaspoon	4.3			17
100 Milk	$\frac{1}{2}$ glass	5	3	4	68
5 Cocoa	1 teaspoon	1.9	1.1	1.5	26
10 Sugar	2 teaspoons	10			40
100 Stewed fruit with sugar	$\frac{1}{2}$ cup	40	1		164
		72	16.8	14.8	488
Total		187.9	40.1	56.7	1422
SUPPER ALTERNATIVE					
150 Milk	$\frac{3}{4}$ glass	7.5	4.5	6	102
10 Sugar	2 teaspoons	10			40
10 Farina	2 teaspoons	8	1		36
5 Butter	$\frac{1}{2}$ square			4.3	39
100 Milk	$\frac{1}{2}$ glass	5	3	4	68
5 Cocoa	1 teaspoon	1.9	1.1	1.5	26
10 Sugar	2 teaspoons	10			40
100 Stewed fruit with sugar	$\frac{1}{2}$ cup	40	1		164
		82.4	10.6	15.8	515

In planning a diet for reduction of body weight, the following principles should be observed:

1. The total caloric intake should be lowered to the basal requirements.

2. The level of the basal metabolic rate should be kept high by:

- (a) A high protein content of the diet.

- (b) Muscular activity.

- (c) Thyroid extracts when the basal metabolism is low.

3. Limitation of salt and water intake.

4. The diet should contain bulky foods for satiety.

In planning a diet for undernutritional states, the following should be observed:

1. A high caloric intake, sufficient to cover the daily energy needs (in actively growing children, this may be 100 to 150 per cent above the actual basal requirements.

2. The basal metabolism should be kept at a low normal plane by:

- (a) A low protein content in the diet.

- (b) Decreased muscular activity.

- (c) Luminal in certain cases.

3. Insulin may be used to stimulate appetite (hospitalization advised here).

4. The diet should be concentrated.

Basic diets for reducing and for gaining weight are given. Additional 100-calorie portions of foods are listed, which may be added to the diet as required to meet the caloric needs of the individual child.

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Chart 2 is the basic diet used for our undernourished children. It contains about 1400 calories, and is given to a child with a basal metabolism of about 700 calories. It contains about 10 per cent protein, 50 per cent carbohydrate and 40 per cent fat. The foods are as concentrated as possible, as these children are usually "small eaters." Additional foods are given in 100-calorie portions, which may be added to the basic diet as required. These foods are planned with an eye to low protein, high carbohydrate content. Carbohydrates are tied up with water retention, have a low specific dynamic action, spare body protein and glycogen, and are easily digested.

A short list of vegetables containing 4 per cent, and also 8 per cent carbohydrate is added; also fruits containing 10 per cent and 15 per cent carbohydrate. These may be substituted for those mentioned in the basic diets (Chart 3).

These diets are merely suggestive. No attempt has been made to give an exhaustive list of foods and food values. For this purpose there are any number of good cook books and dietaries available.

SUMMARY

Abnormal nutritional states—undernutrition and over-nutrition—in children, are defined and briefly discussed.

Normal nutrition depends on the total daily metabolism which has four components:

1. The basal metabolism.
2. The energy required for muscular activity.
3. The specific dynamic action of foods.
4. The requirements in childhood, for growth and development.

The addition of these four factors gives the total sum of the daily metabolic needs of the child. Normally a nutritional state is maintained when caloric intake is sufficient for these four energy needs. If an excess is taken, that excess will be stored as body fat. In the event that less is taken, there will be a negative energy balance with loss of body weight.

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per cent. Blood chlorides 235 mg. per cent. Child was immediately given a clysis of saline solution and an intravenous injection of glucose, the intravenous being continued for several hours. Immediately thereafter the child was given a blood transfusion of 80 cc. citrated blood and the general condition improved markedly. Because of the high CO_2 and low blood chlorides, the convulsions were felt to be due to a gastric tetany (loss of hydrochloric acid followed by alkalosis). The following day the child was given another transfusion of 60 cc. of blood and appeared much better. He was put on small frequent concentrated feedings and did not vomit. CO_2 taken the second day after admission was 100 volumes per cent; blood chlorides were 385 mg. per cent. On the second day after admission distinct peristaltic waves were seen crossing the abdomen from left to right. This time a definite mass under the liver could be felt and a diagnosis of pyloric stenosis was made. With parenteral fluid the general condition of the child improved. CO_2 the following day was 85 volumes per cent and the blood chlorides had gone up to 485 mg. Calcium and phosphorus were normal. Child was put on thick cereal feedings and atropine but the vomiting persisted. CO_2 at this time had come down to 79 volumes and the blood chlorides had gone up to 540 mg. The child was given another transfusion of 50 cc. of whole blood. Just prior to this time the temperature had risen to 105° which was probably due to the atropine.

Six days after admission the child was felt to be in good condition and a Rammstedt operation was performed. Two hours after the operation the child was started on small amounts of water, and milk then slowly added. From then on the child progressively improved. The diet was increased very slowly not only in quantity but also in quality. The wound healed very rapidly and uneventfully. The weight increased, so that at time of discharge, five weeks after admission, the child weighed 2 pounds $5\frac{1}{2}$ ounces more than on admission, was doing well and had stopped vomiting. The CO_2 combining power of the blood was 42 volumes per cent and the blood chlorides were 540 mg. per cent.

Case II.—W. W., seven weeks of age, was admitted with the chief complaint of vomiting for four weeks. First child of normal parents. Full term, normal delivery. Birth weight 7 pounds 9 ounces. Present weight 8 pounds 12 ounces. Breast fed three weeks with complementary feedings of whole milk and water dilutions.

Present Illness.—Four weeks ago (at age of three weeks) the child began to vomit. The vomiting occurred immediately after or during feedings. The vomitus shot out with considerable force. No blood in the vomitus. Three weeks ago he was given thick cereal feeding with some improvement. Luminal was prescribed and continued to the present. Atropine also was given. Four weeks ago the weight was 9 pounds 1 ounce, one week ago 8 pounds 4 ounces, present weight 8 pounds 12 ounces.

One week ago and again five days ago attacks occurred when the child became rigid, the neck extended, the eyeballs rolled back. Since then no spasms or convulsions have occurred.

Bowels markedly constipated.

CLINIC OF DR. MURRAY H. BASS

MT. SINAI HOSPITAL

VOMITING AND CONVULSIONS IN THE NEWBORN INFANT WITH SPECIAL REFERENCE TO TETANY

My purpose in this clinic is to call attention to two types of illness in very young infants, characterized by severe vomiting, both of them leading to very serious conditions with grave disturbance in the body chemistry and both of them amenable to appropriate treatment. The first of these conditions is pyloric obstruction accompanied by alkalosis; the second is a tetany-like syndrome appearing in the newly born infant.

Case I.—A six-week-old infant, admitted September 8, 1932, with a history of vomiting practically since birth. Child was apparently doing fairly well for the first three weeks of life, gaining weight, but three weeks prior to admission vomited persistently and lost three pounds over this period. Mother noticed peristaltic movements over the abdomen. The stools since birth were hard and slimy, usually about one a day. Child had one movement on the day of admission. Four days before admission the child had a convulsion of the upper extremities and the morning before admission a generalized convulsion.

Examination on admission revealed a rather apathetic, markedly undernourished, markedly dehydrated child lying quietly in bed. Respirations were slow and shallow. The eyes were sunken; the fontanel was depressed. Child had a shrill cry. While being examined the child had a generalized convulsion lasting four to five minutes. There was no carpopedal spasm. Turgor was extremely poor. Under the liver to the right of the midline questionable mass about the size of a small nut could be felt. Liver was felt about two fingers below the free border. There were no peristaltic waves seen at this time. Child was slightly spastic. The reflexes were slightly hyperactive. There was no Chvostek's sign or Trousseau's sign. Diagnosis was made of marked dehydration and vomiting; pyloric stenosis with gastric tetany and a possibility that the child might have had a cerebral birth injury with resulting convulsions and vomiting.

Temperature on admission was normal. Blood count revealed a hemoglobin of 65 per cent. White blood cells 11,200 with 84 per cent polynuclear neutrophils, 17 per cent lymphocytes. Urine showed 2 plus albumin, occasional granular casts and occasional white blood cells. CO_2 was 112 volumes

sively worse till the seventh week of life when convulsions made their appearance. This infant did not look dehydrated, and had not lost much weight, but on account of the history of convulsions, chemical examinations were ordered as in the first case, with very similar results. The CO_2 combining power of the blood was 82 volumes per cent, the total blood chlorides were 410 mg. per cent, and the calcium was 10 mg. Again we have here a condition of alkalosis.

During the past two decades much light has been shed upon the chemical pathology of intestinal obstruction, with the result that where formerly we looked upon pyloric stenosis as a purely mechanical condition we are now in a position not only to realize the abnormal local mechanical status in the stomach and intestines, but we understand to a much fuller degree exactly what effect the mechanical disturbance at the pylorus is producing upon the individual's entire physiology. The clinician therefore now must look upon such an infant, not merely with his attention upon the narrowed pylorus, but he must realize that enormous changes in body chemistry have been initiated and that these changes in themselves may become severe enough to cause the death of the patient, and that therefore their treatment may be more imperative than the mechanical relief of the intestinal obstruction.

As far back as 1915 Wilson¹ and his coworkers showed that alkalosis might be a possible cause of tetany. In 1918 McCann² showed that the plasma CO_2 combining power of the blood was greatly increased after experimental pyloric obstruction. In 1920 McCallum³ showed that the diminution in blood chlorides was of great importance, and stressed the fact that the resulting tetany could be prevented by intravenous injection of sodium chloride. Many other investigators have continued this line of investigation as for example, Hartmann and Smyth⁴ who published a large series of cases of vomiting in infants and children, showing very marked metabolic disturbance. They showed that "as a result of the vomiting chloride is lost. As the chloride diminishes in the blood, bicarbonate is retained and compensates at least in part for the

Physical Examination.—A well-developed somewhat undernourished white male infant; very drowsy but not acutely ill. Turgor is only fair. There is slight dehydration but definite evidence of loss of weight. Except for exceedingly large waves passing across the upper abdomen from left to right, the physical examination is negative. There is no carpopedal spasm, no Chvostek's sign, no Trousseau's sign. No abdominal tumor felt.

10/21: Electrical reactions show hypo- rather than hyperirritability. No anodal contraction even with strong current. Child put on whole milk mixture with atropine 1/500 by hypodermic a. c. Temperature rose to 104.4°. No vomiting.

10/22: Hemoglobin 70 per cent.; red blood cells 3,460,000; white blood cells 16,600; differential count was normal. Wassermann test negative; CO₂ 82 volumes per cent; calcium 9.5 mg. per cent; blood chloride 410 mg. per cent; urine clear, acid, 1.012, albumin plus; occasional hyaline and granular casts; 4 to 6 white blood cells and occasional red blood cells. Coarse tremor of both upper extremities but no convulsions.

10/23: Clysis 145 cc. normal saline.

10/24: General condition only fair. Still running fever. Vomited several times. Coarse tremor still present. CO₂ 81.5 per cent; blood chloride 530 mg. per cent; stools have become frequent and the child has lost 7 ounces in weight; transfusion 90 cc. whole citrated blood.

10/25: Continuous intravenous 5 per cent glucose in Ringer's solution; operation: Rammstedt, large pyloric tumor split.

10/29: Good recovery. Put on breast milk for two days. Then gradually to whole milk dilutions. Stools good; gaining in weight; temperature normal.

11/4: CO₂ 56 volumes per cent; blood chlorides 580 mg. per cent; uninterrupted recovery.

From the description of these cases it will be seen that we were dealing with typical cases of pyloric obstruction. In both cases moreover convulsions had occurred. Case I had several general convulsions both before and after hospitalization, in fact it was the convulsions and not the vomiting which led the mother to hospitalize the child.

On account of the convulsions and dehydrated condition of the baby it was decided to investigate its chloride metabolism, its CO₂ combining power and blood calcium. The figures for the CO₂ were greatly increased (112 volumes per cent). The blood chloride was greatly diminished (235 mg.). The calcium was normal. We have here an infant in a condition of alkalosis.

Case II gave a perfectly typical history of pyloric stenosis beginning at the age of three weeks and becoming progres-

His findings corroborate those of previous investigators. He believes that the hypochloremia is of greater degree in pyloric stenosis than is found in other types of vomiting and that because of this, it may be used as a method of diagnosis of this disease.

From the foregoing we may therefore conclude that in the two cases we have described, the following series of changes has occurred, the excessive vomiting has led to a loss of sodium chloride, but the chloride ion is much more powerful as an acid than is the sodium chloride as a base. The result is that the body is depleted of acid and that the chloride of the blood is diminished. This loss is chiefly replaced by carbonic acid which may rise to great excess and which combines with sodium to form bicarbonate. Consequently the alkali reserve of the plasma increases while the chloride diminishes, producing a condition of primary alkali excess (Peters and Van Slyke). In cases where for any reason hyperventilation now supervenes, CO_2 is excreted in excess and thus the balancing power of pulmonary ventilation is lost and the alkalosis previously compensated, may become uncompensated with a real shift in the pH of the blood toward the alkaline side.

This alkalosis should theoretically produce tetany. In experimental obstruction tetany has been produced. In older individuals gastric tetany with carpopedal spasm is of no great rarity. However in our cases we were unable to prove tetany present. Both infants had convulsive seizures, but neither showed Trousseau's nor Chvostek's sign and in the second case electrical reactions appeared to be normal. All authors comment on this peculiarity. Thus Graham and Morris say: "The presence of such a degree of alkalosis as suggested by the high CO_2 values would lead one to expect the frequent occurrence of tetany. Signs of increased muscular irritability, as a matter of fact, have been reported frequently in high intestinal obstruction in the adult, as well as that produced experimentally in dogs. Convulsions, although said to be common, by some observers, are in our experience rare in pyloric stenosis of infancy. In only two cases was there any such

deficiency in electrolyte, so that the salt content remains nearly normal. When the loss of sodium chloride in the blood is not fully replaced by sodium bicarbonate, the nonprotein nitrogen becomes elevated, to the extent of keeping (theoretically) osmotic pressure normal. When the sodium bicarbonate content of the blood is high, there is a depression of respiration sufficient to lead to the accumulation of enough carbonic acid to maintain an approximately normal $\frac{\text{H}_2\text{CO}_3}{\text{NaHCO}_3}$ ratio, so that the reaction of the blood ($p\text{H}$) is usually nearly normal. Following increased pulmonary ventilation from any cause, however, the blood becomes abnormally alkaline and manifestations of tetany may appear."

In 1929 Graham and Morris⁵ made chemical studies on a large series of pyloric stenosis cases and obtained similar results. They also stressed the fact that clinically, infants who had vomited for a long time, would show marked diminution in the respiratory rate. Not only were the respirations slow but they were very shallow and often appeared to be of the intermittent type (Biot breathing). They point out that there is a very constant relation between the CO_2 content and the respiratory rate and in their opinion this is quite characteristic of pyloric stenosis.

In a second communication published in 1931 Morris and Graham⁶ showed by chemical analysis of the organs of infants who had succumbed to pyloric stenosis that there is a partial chloride vacuum in the tissues—the sodium chloride content of various organs being far below that of the normal. They believe that this can be corrected by the administration of saline solution, which if continued may lead to edema due to excessive retention of chloride, even when the chloride content of the blood is normal. They also showed, as we found in the cases presented, that restoration of the blood chlorine content to normal does not result in immediate correction of the alkalosis as is evidenced by the persistence of the high CO_2 content and depressed breathing.

The most recent work in this field is by Edgar Schmor.⁷

of convulsions, cases of pyloric stenosis with alkalosis, such as we have described cannot be classified as "tetany."

There is another group of cases to which I wish to call attention, namely, newborn infants who in the first few days of life show the following characteristic symptomatology: they refuse food, begin to vomit, run high temperature, become distended and then have multiple convulsions. Together with Dr. Samuel Karelitz I reported three such cases.⁹ The following is the history of one of these cases.

Case III.*—A. C., a girl, the first child of normal parents. Born at term, weighed 7 pounds 7 ounces. Labor was somewhat difficult because of a rigid perineum. An episiotomy was performed. The child was born with one coil of cord wound around her neck but showed no ill effect from it.

In her first day of life she vomited, first some mucoid material, subsequently everything offered. The vomiting continued the next day and became projectile in character and followed immediately after taking water or a formula. The child was put to the breast but would not nurse. The nurse noted that the child was very restless, was nervous, and cried frequently and with a shrill voice. On the third day, vomiting continued and the temperature rose to 103.6° F. Peristaltic waves, from left to right, were noticed, and the abdomen became distended. A consulting pediatrician suggested the diagnosis of pyloric stenosis and advised atropine and subcutaneous injections of dextrose solution. No improvement followed the administration of atropine or dextrose solution. On the fourth day of life, the temperature was 105° F.; her abdomen was markedly distended; the child was markedly hypertonic and responded to noises or to being touched by a generalized jerk or spasm. The Chvostek sign was very active and the Trousseau phenomenon also was positive. There was a generalized increase of reflexes. When offered fluid, the child took it with much desire but vomited it almost before it had time to enter her stomach. Whole milk with 17 per cent added sugar was just as futile. A rectal drip of 5 per cent dextrose solution was retained. A tube entered the stomach with ease and a return of bile-stained fluid was seen. That, plus the fact that meconium had been passed and was also bile-stained suggested that there was no complete intestinal obstruction. To rule out a possible birth injury, a lumbar puncture was done. The fluid was clear, under normal pressure, and contained only 6 cells.

However, despite the symptoms suggesting tetany, the diagnosis of incomplete intestinal obstruction was made. A consulting pediatrician concurred and a surgeon was called. Before the surgeon arrived, barium was given in a small amount of milk and its progress through the stomach and intestine was observed by fluoroscopy and roentgenograms. Fluoroscopy and roent-

* This case is quoted from the article by Bass and Karelitz: Tetany Accompanied by Hyperpyrexia in the First Days of Life, which appeared in *Tour. Amer. Med. Assoc.*, Nov. 7, 1931.

history obtained. In one of these laryngismus was an associated symptom. In no case tested was the neuromuscular excitability increased, as one might have expected. The reason for this absence of the signs of tetany may in part be due to the increased blood calcium content which we have found as high as 14 mg. per cent."

In my cases, both of which had convulsions, there was no increase in calcium in the blood.

Peters and Van Slyke⁸ also comment on the question of tetany and say: "Certainly active tetany is a comparatively rare occurrence in clinical pyloric obstruction even in cases with extremely elevated plasma bicarbonate. Hartmann believes that it occurs only when because of excitement or some other stimulus respiratory activity becomes unduly augmented. The hypochloremia, however, appears to render these patients peculiarly susceptible to the effects of overventilation. Consequently slight hypernea suffices to drive them into tetany."

Schmor also believes that the lowering of pulmonary ventilation keeps enough CO_2 in the blood to counteract the alkali formed so that the alkalosis is compensated and the reaction of the blood remains constant, preventing the appearance of real tetany.

Since all the characteristic signs of tetany, including hyperirritability to the electric current were absent in the cases here presented I am loath to call them cases of tetany. Clinically they did not behave like tetany, except for the fact that they had convulsions; though their blood chemistry suggests that they should show tetanic manifestations, on the basis of the findings in adults. It might be argued that perhaps the newborn infant does not react to alkalosis in the same manner as the adult. This is not necessarily true for I myself inadvertently caused clinical tetany, with positive Chvostek's sign, carpopedal spasm and convulsions, in a six-week-old infant suffering from pyelitis. Excessive doses of alkali were prescribed which caused the appearance of typical tetany. When the alkali was stopped the tetany immediately disappeared.

One must conclude therefore that in spite of the presence

quite characteristic. Added to this is the prompt response to calcium therapy.

In spite of these facts our right to call this condition tetany, was questioned, for infantile tetany was not supposed to occur in the newborn. Here and there in the course of years a few cases of undoubted tetany have been described. Quite recently I have been informed of two cases* showing this characteristic syndrome of vomiting, hyperpyrexia and convulsions in which blood calcium were shown to be 7.3 mg. and 5.3 mg. per cent respectively. This fact I believe would prove this disease to be true tetany and would give a real reason for the dramatic recovery after calcium administration.

Pediatricians and obstetricians should be aware of this condition since it is one which threatens life but is easily controlled by appropriate treatment.

I have attempted to describe two clinical syndromes in newborn infants both of them characterized by vomiting and both having convulsions. The first occurs in infants suffering from pyloric stenosis and is due to alkalosis caused by loss of chlorides. The important factor in the therapy is to replace the lost chlorides, best by intravenous or subcutaneous infusions. This should be done whether the case is to be treated medically or surgically, for the chloropenia itself and the resulting alkalosis are serious conditions, fraught with real danger to life itself.

The second group of cases I have described also vomit and have repeated convulsions. These children manifest evidences of tetany, in some cases show a low blood calcium, and are promptly cured by the administration of calcium by the intravenous or intramuscular route.

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* These cases were observed and will be published respectively by Dr. J. L. Rothstein of New York City and Dr. David Gaberman of Hartford, Conn.

genograms showed a marked cardiospasm, but some of the barium entered the stomach immediately and within a few minutes was in the duodenum. The barium reached the cecum in about five hours but did not pass this part. Enemas previously given were without return, either fecal or gaseous. A barium enema was given, and within a few minutes was expelled with explosive force. Two balls of barium traced from the small intestine were found, thus proving definitely that no intestinal obstruction existed. Spasm of the large intestine was also visible on the roentgenograms. The cardioplasm was still present after twenty-four hours. Several convulsions were observed in the next twenty-four hours and were characterized by carpopedal spasm and a shrill cry. On the fifth day of life the temperature was 106° F., the distention had recurred, the signs of tetany were even more marked, and vomiting continued to be severe. A formula of human milk plus 10 per cent sucrose and 8 per cent farina was made into a thick cereal and given in 1-ounce feedings every two hours. That was retained, and for the first time her weight remained stationary—6 pounds and 5 ounces. At midnight, July 21, her fifth day of life, the temperature was 107.4° F. and she had several violent generalized convulsions. Her temperature dropped to 104° F. after baths, enemas and wet packs were given. Hyperirritability, restlessness, hyperacusis, positive Chvostek's sign, Trousseau's phenomenon and typical carpopedal spasm continued. The formula was stopped for fear that it may have contributed to the apparent progress of her illness. July 22, her sixth day, the temperature was 105° F., the Chvostek sign, Trousseau's phenomenon and shrill voice were still evident, and vomiting and spasms continued. Blood was drawn for chemical analysis and 8 cc. of calcium gluconate was injected intravenously. The effect was dramatic; the hands and feet, formerly very spastic, suddenly relaxed; she became more alert and brighter; her temperature began to drop; the vomiting diminished, and, in twenty-four hours, the Chvostek's sign was barely obtained. The child had slept well for the first time; vomiting occurred only occasionally and no more spasms were observed. The child began to nurse well, she retained water, the temperature became normal, and from then on the child made excellent progress. A gastrointestinal series, one week later, revealed that the cardiospasm, though still present when food was given, cleared up in a few minutes.

The child had pertussis at four months and hardly vomited. She is now ten months old, weighs 26 pounds and is neurologically and otherwise a perfect baby. Blood calcium was 8.5 just before the calcium gluconate was injected.

In classifying such a case, just as in the cases of pyloric stenosis, we were in some doubt as to whether the term "tetany" was justified. It is true that in this one case a single blood calcium determination showed 8.5 mg., a figure somewhat high for manifest infantile tetany. The clinical picture however is typical of tetany—the Chvostek's sign, the Trousseau's sign, carpopedal spasm, laryngismus and convulsions are all



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leagues for the hard of hearing. The term "hard of hearing" is taken to mean that the person has become crippled, to some degree, by loss of hearing after the establishment of normal speech and does not, in consequence refer in any way to the deaf. The word "deaf" is reserved for persons who have never consciously heard and who have been educated in a special way. These are comparatively few in number when compared with the vast army (some 10 million in the United States) of those with more or less hearing impairment. These leagues, numbering over 120 throughout the country, are health centers for the hard of hearing and as such become most valuable to the otologist for assistance in readjusting his hard of hearing patients and should be used by the profession more than they are. Full information regarding the functioning of these leagues may be obtained from the American Federation of Organizations for the Hard of Hearing, Inc., 1537 35th Street, N. W., Washington, D. C.

The cases which are assembled here have been selected to illustrate this idea of the modern clinic. They are drawn from the case files of the New York League for the Hard of Hearing, which was founded in 1910, and is the largest and oldest local organization in this specialized field. It has, as well, what the writers consider a model set-up for its work in the fact that the Board of Directors and the membership are almost entirely hard of hearing persons and the staff of social workers 100 per cent so. That is, the proportion of readjusted persons actively engaged is high.

Before proceeding to the description of cases let us recall the mental effects arising from impaired hearing. The two great divisions of depression and suspicion embrace many varieties and degrees of severity. Many of these depressed or suspicious people, especially if they meet with adequate encouragement and the substitution of new interests for those which may no longer be pursued, can and do make what Menninger calls "the constructive compromise." They may even enter into a richer life of which the satisfactions are greater than those formerly experienced in an unhandicapped state.

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SOME PROBLEMS ENCOUNTERED IN THE MANAGE-
MENT OF PATIENTS WITH IMPAIRED HEARING

SCIENTIFIC progress, we all admit, is changing many of the facts, long accepted and built into our general professional knowledge and opinion. It is also giving us a broader interpretation of many expressions, for example, the word *clinic*. Starting centuries ago with the Greek word for *incline*, it became—still in the Greek—a word for sick bed; that meaning, in our present-day interpretation, has become a place where medical students are instructed and where free patients are treated, and where physicians may add to their experience through their voluntary service. The clinic, we perceive, is a place for study.

The study of our cases today does not stop with the medical aspect of them. We investigate the patient's mental health and, through our social workers, study his personal and working environment. In no department of medicine is there a greater need for such extended study as in the specialty of otology in cases where the sense of hearing has become impaired. This arises from the characteristic and often unusual emotional responses to this particular condition which are all too seldom taken into consideration either by the otologist or the family physician. These cases, however, require not only the care and treatment of the otologist, but if they are to be emotionally readjusted (and frequently vocationally rehabilitated) they may also require the more expert advice of the psychiatrist and certainly the cooperation of the family physician and such specialized social workers as are found in the

Diagnosis: Bilateral complete loss of hearing. Run down by automobile in August, 1929. Fractured skull, cerebral hemorrhage, traumatic deafness. Hospital care six weeks.

Prognosis: No improvement possible.

Recommended: Lip reading, occupational retraining.

Emotional state: Healthy.

Former occupation: Doorman, hotel footman—held positions four to five years.

Married: Two children, twelve and four years of age.

This proved a comparatively simple case for vocational rehabilitation. After considerable discussion between the League's employment bureau and the State Bureau of Rehabilitation as to a suitable occupation it was decided to refer him for training in painting and decorating, some of his former employers having undertaken to find work for him. He entered the free evening school lip reading classes (City Department of Education). One interesting point in this case was the fine cooperation given by Mr. C.'s wife and mother-in-law which doubtless assisted him in retaining his good mental health.

Case III.—M. W. F., aged twenty-three, female, stenographer. Had mumps without complications at ten years of age. A submucous reaction

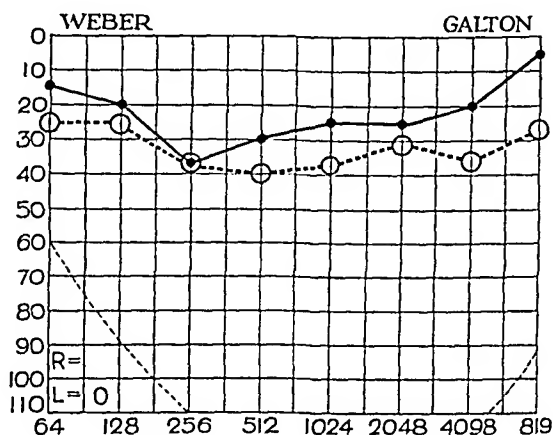


Fig. 231.—Audiometer Test.

and sinus operation two years ago. Hearing impairment began in both ears three years ago. There were perforation scars in both ear drums with some resultant retraction and thickening.

Audiometer test.

Examined: January, 1933.

Diagnosis: Chronic catarrhal otitis media.

Prognosis: Unfavorable as to hearing improvement.

Recommended: Lip reading, League activities.

Emotional state: Constructive.

But this happy ending does not always occur. Even as the utmost intelligent and scientific effort of the otologist may fail to improve the patient's ear conditions, so the social readjustment may hang fire (or in some cases actually regress) somewhere along the line of progress toward the hoped-for conclusion.

Happily, however, the combined efforts of the otologist, the psychiatrist, the family physician and the specialized social worker serve to stimulate the hard of hearing individual to energize his remaining faculties to overfunction in an effort to overcome his hearing handicap.

The citation of the following case histories will serve to illustrate some of the mental quirks often observed in patients with severe hearing impairment—together with the results of our attempts to rehabilitate.

Case I.—W. B., aged thirty-two, female.

Diagnosis: Otosclerosis.

Prognosis: No hearing improvement possible.

Emotional state: Healthy.

Referred to: The New York League for the Hard of Hearing by the Metropolitan Life, October 3, 1923.

Occupation: Public school teacher—given up on account of hearing impairment.

Recommended: Patient was advised to use hearing aid and to adopt lip reading and vocational retraining.

Data regarding this young woman are few. Her case is cited because of her vigorous and healthy reaction to an unfortunate and costly experience. This woman had for a year been treated by a person who is characterized as a quack by the American Medical Association. She at length became aware that her hearing was steadily losing ground. She was referred by the league to an otologist of high standing and received general advice as to her future. Returning to her home, she made contact with the Bureau of Investigation of the American Medical Association and compiled an excellent group of comments criticising so-called "finger surgery" for the cure of deafness. Later she also prepared an article which was published in *Hygeia*.

We have heard nothing more about Miss B. but have no doubts that such a healthy-minded woman succeeded in working out a satisfactory readjustment.

Case II.—C. C., aged thirty-eight, male.

Examined: November 14, 1930.

Diagnosis: Bilateral complete loss of hearing. Run down by automobile in August, 1929. Fractured skull, cerebral hemorrhage, traumatic deafness. Hospital care six weeks.

Prognosis: No improvement possible.

Recommended: Lip reading, occupational retraining.

Emotional state: Healthy.

Former occupation: Doorman, hotel footman—held positions four to five years.

Married: Two children, twelve and four years of age.

This proved a comparatively simple case for vocational rehabilitation. After considerable discussion between the League's employment bureau and the State Bureau of Rehabilitation as to a suitable occupation it was decided to refer him for training in painting and decorating, some of his former employers having undertaken to find work for him. He entered the free evening school lip reading classes (City Department of Education). One interesting point in this case was the fine cooperation given by Mr. C.'s wife and mother-in-law which doubtless assisted him in retaining his good mental health.

Case III.—M. W. F., aged twenty-three, female, stenographer. Had mumps without complications at ten years of age. A submucous reaction

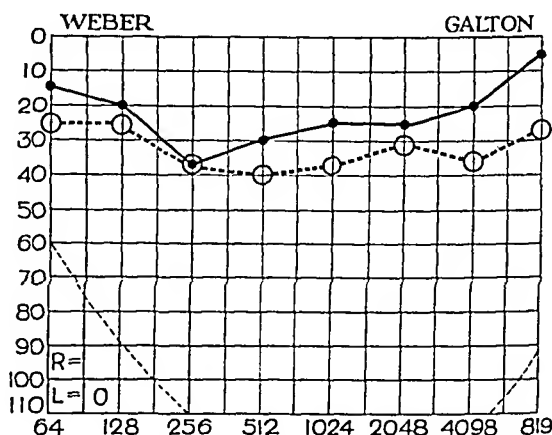


Fig. 231.—Audiometer Test.

and sinus operation two years ago. Hearing impairment began in both ears three years ago. There were perforation scars in both ear drums with some resultant retraction and thickening.

Audiometer test.

Examined: January, 1933.

Diagnosis: Chronic catarrhal otitis media.

Prognosis: Unfavorable as to hearing improvement.

Recommended: Lip reading, League activities.

Emotional state: Constructive.

This young woman grasped her opportunities for readjustment eagerly. She became a favorite in League recreation circles and with another girl as classmate entered a private school of lip reading. The fact that her home is in a suburban town offered no obstacle to her evening work or play.

Miss F. has been unusually fortunate in her work environment. Her employer knows she is hard of hearing, adapts his voice to her handicap when giving dictation. This is her first job and she has held it since she was eighteen, a fact which indicates her value to the firm. She has discussed a possible change of occupation with the League's vocational counselor who advises her to remain where she is unless some change in her hearing renders retraining necessary.

Case IV.—L. S., aged thirteen, female, recommended by her teacher.

Examined: January 16, 1932. Had all the exanthemata. Takes cold easily. Tonsils and adenoids removed January, 1932. Mother hard of hearing

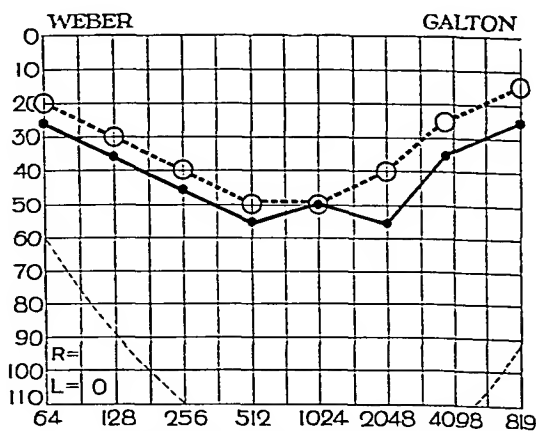


Fig. 232.—Audiometer Test.

following severe shock. Patient is underweight and nervous, probably the result of overstrain in efforts to keep up school work.

Audiometer test.

Recommendation: Complete physical examination and treatment, also lip reading.

This child entered Junior High School, where she had lip reading in a special project class through cooperation with the New York League for the Hard of Hearing and continued her instruction in the League's own demonstration school. Her impaired hearing attracted the attention of the high school placement counselor, who took up her case with the State Bureau of Rehabilitation regarding her vocational education. As she was already under League care, the State Bureau discussed the girl's future with the League, particularly regarding her choice of stenography as an occupation. It will be recalled that Alfred Adler, the psychiatrist, calls attention to the fact that



pondence which confirmed that her misfit in the League (for ten years) arose from her poor selection of acquaintances. She came around, wished to do the League's publicity work and was encouraged to study, the publicity worker consenting to accept her as a volunteer if she did so. (This also fell through.) As she was unemployed, she was encouraged to have an interview with our employment bureau and she registered there. For some ten years and at the present time she has been getting considerable pleasure and satisfaction through a correspondence club conducted by the American Federation of Organizations for the Hard of Hearing.

Miss F. is restless, unsatisfied with anything within her powers to do or with associates within her powers to meet and attract. She writes well but will not work at it; shows marked irresponsibility and feelings of superiority. Needs intensive lip reading practice but will not go to evening school. Her impaired hearing does not seem to weigh heavily upon her. She may have a real capacity for leadership buried under her assumption of superiority and her irresponsibility; but she will always suffer from her inability to meet normally-hearing people with ease. Her incomplete readjustment confines her socially to the handicapped group.

These cases illustrate the manner in which various elements contribute to the picture of the modern clinical study of the hearing problem. Important as the otologist is, he still is not all; the services which are available to him through specialized service, leagues for the hard of hearing, also assist in attaining his objective, that is, the maximum improvement attainable in the health of his patient.

Since one of the chief obstacles to a constructive readjustment is the frequent unwillingness of the patient to cooperate fully, it may be seen how necessary the social worker's technic is in procuring the desired cooperation.

incomplete and the so-called "ketone bodies," acetone, acetoacetic acid and bethahydroxy-butyric acid circulate in the blood in greater than normal concentrations. Such an acidosis has also been held responsible for the impairment in refraction.² The lipoids of the blood, of which cholesterol and lecithin are the chief representatives, are often found increased in diabetes mellitus. It has been shown that insulin treatment tends to lower the concentrations of these bodies in the blood.

Water Metabolism.—The water metabolism of the body is also changed in diabetes mellitus and the cellular permeability of the tissues is decreased. Insulin has been shown to increase tissue permeability.

The Relation of Human Aqueous and Blood Sugar.—In order to estimate the etiologic importance of hyperglycemia for the more frequent occurrence of senile cataract in diabetics, the ratio of sugar in the blood to sugar in the aqueous humor in normals and in diabetics under varying conditions should be known. For this purpose, we undertook to study the ratio in the sugar concentration between the two fluids as well as the rate of increase in sugar concentration in the aqueous humor as compared to the blood, following ingestions in the form of glucose or in the form of a mixed meal. The material we present to you today comprises blood and aqueous humor sugar determinations on 48 cases, 23 of which were known diabetics; sugar tolerance tests on 13 patients, carried out on both venous and capillary blood with single determinations of the aqueous humor sugar concentrations of both eyes at different points of the curve; sugar depletion (insulin reaction) tests on 3 cases with determinations of capillary and venous blood sugar and aqueous humor sugar concentrations at two different points of the curve; 5 cases in which the rise in blood sugar following the intake of an ordinary, mixed meal was determined in both capillary and venous blood and again the sugar concentrations of the aqueous humor determined at two different points of the curves. In 10 cases we determined the sugar concentrations of the primary and regenerated aqueous humor.

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CARBOHYDRATE METABOLISM AND CATARACT. A
STUDY OF THE RELATION OF THE SUGAR OF THE
HUMAN AQUEOUS HUMOR AND THE BLOOD*

THE observation is frequently made that senile cataract occurs more often in diabetics than in nondiabetics. Not only is the incidence greater but the onset of the cataract occurs at a relatively earlier age. The increased blood sugar level in diabetics has been held to be the factor responsible for the greater susceptibility to cataract formation. For the purpose of this discussion, cataract may be defined as any opacity of the crystalline lens. To it also are often ascribed the changes in refraction of the eye in diabetes mellitus and it has been shown that a return to a more nearly normal blood sugar level, brought about by insulin treatment, at times may be accompanied by a decrease in the myopia.¹

The Lipoids in Diabetes.—The deficient utilization of carbohydrate in diabetes mellitus is usually accompanied by a disturbance in fat metabolism which may lead to a constant, more or less severe acidosis. Ketonemia and ketonuria are frequently present in the more severe, uncontrolled cases of diabetes mellitus. The oxidation of the fats and fatty acids is

* The data in this contribution were gathered while Daniel B. Kirby was Research Fellow in Ophthalmology for the American Academy of Ophthalmology and Otolaryngology and R. von E.-Wiener was Consultant Research Chemist to the Department of Ophthalmology, Columbia University. The reader is referred to the complete report of the investigations published in the Transactions American Academy of Ophthalmology and Otolaryngology, 1932, pp. 142-213.

like the formation of the lymph with the capillary endothelium as the permeable membrane. The barrier between blood and aqueous humor is far more complex. It consists of the capillary endothelium, the loose meshwork of connective tissue and the epithelium of the ciliary body. The aqueous humor is derived from the blood circulating in the vessels of the ciliary body. Glucose is an active metabolite and the nutrition of the barrier tissues must play a part in the distribution of the glucose between the blood and aqueous humor. In its passage across the barrier it is subjected to metabolic influences and to the probable secretory function of the ciliary epithelium. Vasomotor processes by increasing or decreasing the capillary permeability, as well as hormonal influences on permeability, may affect the blood-aqueous relationship. The diffusion of the sugar must also be affected by its relative concentration in the blood and aqueous. The aqueous humor has an extremely slow circulation and represents the nutrient medium for the nonvascularized eye tissue. Its constituents are therefore also subject to metabolic changes, due especially to the activity of the lens and other tissues.

Estimation of the Human Aqueous Sugar.—We first attempted to determine the relationship between sugar in the blood and sugar in the aqueous humor and the average ratio of these values in nondiabetic senile cataract cases and in those senile cataract cases complicated by diabetes mellitus. Forty-eight patients were thus examined. The examinations were carried out in the afternoon at the Eye Department of the Vanderbilt Clinic. The tests were made one and a half to two hours following the ingestion of the noon-day meal. Following the paracentesis, the patient was allowed to go home, after an hour's rest.

Technic of Anterior Chamber Puncture.—Paracentesis of the anterior chamber of the human eye with removal of the aqueous need not be feared if proper precautions are observed. Local anesthesia is necessary and a speculum to support the lids. Fixation forceps without catch are employed to steady the globe. Fixation is best taken in the upper nasal quadrant

The Factors Influencing the Aqueous Sugar Level.—

The factors which may affect a carbohydrate tolerance curve and which cannot be controlled, should be kept in mind. This was especially important in the elderly age group we dealt with. We know that there is no hexose resorption from the stomach and that the rate of resorption from the intestinal tract varies in different individuals and most likely also in different age groups. Rapid resorption tends to produce hyperglycemia. Again there may be excessive destruction of sugar in the intestinal tract due to abnormal bacterial action. When the rise in blood sugar is determined after the intake of a mixed meal, the character of the food will play a decisive part in the rate of resorption and production of alimentary hyperglycemia.

The Utilization of Sugar.—Ingested carbohydrate material is split to the hexose state in the gastro-intestinal tract and the resorbed hexose is carried to the liver. There it may be either utilized, polymerized to glycogen or be given up to the general circulation. The glucose which enters the general circulation is partly absorbed by the tissues on the passage of the blood from the arterial to the venous circulation. If the liver function in respect to carbohydrate metabolism is below normal less glucose will be held back and more will enter the systemic circulation. Normally the liver is more of a consumer of sugar than a producer, but the liver can form sugar from protein. The relative distribution of glucose in the skin, muscles and blood has been determined.³ The diabetic has relatively more sugar in the skin and less in the muscle than the nondiabetic. Since in our work we determined the sugar concentrations in both venous and arterial (finger-prick) blood, we also obtained an expression of the activity of the tissues in removing glucose from the blood. In old age, in accordance with the diminished vital functions, the sugar tolerance is slightly decreased and this is especially noticeable in the curves determined on finger-prick blood.

The Formation of the Aqueous.—There are several theories as to the forces active in the formation of the aqueous humor. The formation of the aqueous does not take place

Further Study.—We now decided to study the relationship between the sugar concentrations of the blood and the sugar concentrations of the aqueous humor, during sugar tolerance and sugar depletion tests. The tests were carried out under strict supervision in the hospital. In Figs. 233, 234 the composite curves obtained from thirteen tolerance tests are shown. Eleven of these cases had senile cataract, one had chronic glaucoma and one had no eye pathology. Fig. 233 gives the composite curves of the 7 cases which gave normal or old age type curves, and Fig. 234 the composite curves of the 6 cases which gave a diabetic-like response, and which includes the four known diabetics of the group.

Ratio of Aqueous to Blood Sugar.—If you examine these curves you will notice that they show a certain difference aside from the generally decreased tolerance and higher level of the diabetic type curves. You notice that there is a greater difference between the capillary and venous blood sugar curves in the diabetic type curves than in the nondiabetic type, and this difference extends into the later period of the test. Most striking, however, is the difference in aqueous sugar concentration. Thus the average ratio of aqueous humor glucose to capillary blood glucose in the nondiabetic group from 0.55 at the end of the first hour to 0.77 at the end of the two-hour period. The corresponding average ratios in the diabetic group were 0.57 at the first hour and 0.67 at the second hour.

Changes in Concentration of Aqueous Sugar.—The rise in aqueous humor glucose lags behind the rise in blood sugar and this lag is still more pronounced in the diabetic type of curve. In Fig. 233 representing the nondiabetic curves you also notice the line for the aqueous rise taken in the first hour. While it is difficult to judge from the limited material, we have found in other studies as well that the fasting aqueous humor glucose concentration approaches that of the blood most closely. Hence, we feel justified in postulating a relatively more rapid and more brief rise in aqueous humor sugar in the nondiabetic type of individual following the ingestion of sugar.

and the syringe (tuberculin 1 cc.) with a 27-inch gauge needle is entered horizontally opposite the fixation. If the syringe and needle are rotated in a drilling fashion, the needle may be introduced without even dimpling the cornea, without undue force or sudden jump into the anterior chamber. The anterior chamber fluid called the primary aqueous humor may then be withdrawn in amounts varying from 0.1 to 0.4 cc. The method is painless. After paracentesis a light dressing is applied. This is removed in twenty-four to forty-eight hours, at which time the anterior chamber has returned to its former depth. In a few cases there were subconjunctival hemorrhages at the site of fixation. In one case of old iritis there was a flaring up of the process for a few days. Otherwise, the post-operative course of these patients was uneventful.

Results in Forty-eight Cases.—Of these 48 patients 23 were diabetics under treatment. We found no striking difference in ratio between the diabetic group of patients and the nondiabetics. In fact averaging the ratios of the two groups there is practically no difference as you can see by the table (Table 1). As all of the diabetics were under treatment and were not very severe cases, the differences in blood sugar concentrations are also not very great.

TABLE 1

Number of cases.	Average age.	Average blood sugar in mgs. per 100 cc.	Average aqueous sugar.	$\frac{\text{Aqueous sugar}}{\text{Blood sugar}}$ av. ratio.
20 senile cataract.....	60	126	98	0.78
5 without cataract....	44	140	112	0.80
20 senile cataract and diabetes	61	146	118	0.81
2 diabetes without cataract.....	53	135	120	0.88

The individual variations in the ratio in the nondiabetic group were between 1 and 0.61 and in the diabetic group between 1.05 and 0.63. The results show that there is a deficit in the aqueous humor glucose as compared with that of the blood following carbohydrate intake.

blood sugar level rises during a transient hyperglycemia which determines the extent to which the glucose in the aqueous will increase, but the duration of the hyperglycemia.

The Effect of Insulin Injection.—We next attempted to determine how rapidly the aqueous humor glucose concentration adapts itself to a rapid fall in blood sugar such as is caused by the injection of insulin. The sugar depletion or insulin test consisted of the administration of a small dose of insulin, usually 10 units, one hour after the ingestion of a meal containing a moderate amount of carbohydrate, and the determination of the blood sugar levels, before the administration of the insulin and at regular intervals thereafter for a total period of two to two and a half hours. If the results are plotted in the usual manner, they approach the reverse of a tolerance curve and may be used to evaluate the carbohydrate metabolism.

The normal response to a small dose of insulin given in this manner is a rapid, but not very marked fall in blood sugar concentration during the first hour of the test, followed by a recovery of the normal blood sugar level during the second hour. The curve is steepest during the first thirty minutes after the insulin injection, the lowest point reached by the blood sugar should not lie below 55 mg. per 100 cc. In the diabetic there is a certain retardation in the insulin action and the blood sugar may even continue to rise in the first half-hour period. The fall in blood sugar is prolonged and extends into the later periods of the test.

The Effect of Insulin Injection on Aqueous Sugar.—The changes in sugar concentration, both in the venous blood and in the finger-prick blood and the coincident changes in aqueous humor glucose were determined in three diabetics, two of whom had cataracts and in one of whom no eye pathology was found. The curves obtained in these 3 cases are shown in Fig. 235. To avoid confusion only the capillary blood sugar curves and the aqueous sugar determinations are plotted. You notice that the fall in blood sugar extends throughout the test period. In case A. S., there is a slight rise during the first

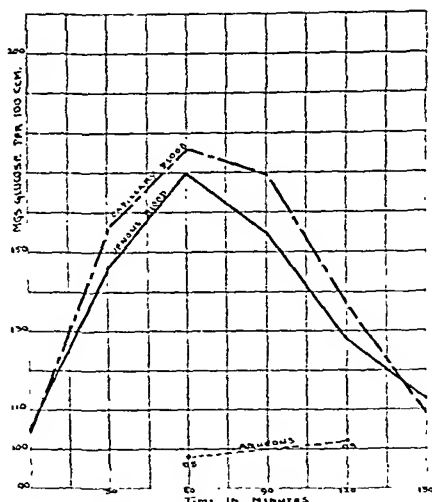


Fig. 233.—Composite curves of sugar tolerance tests on six nondiabetics.

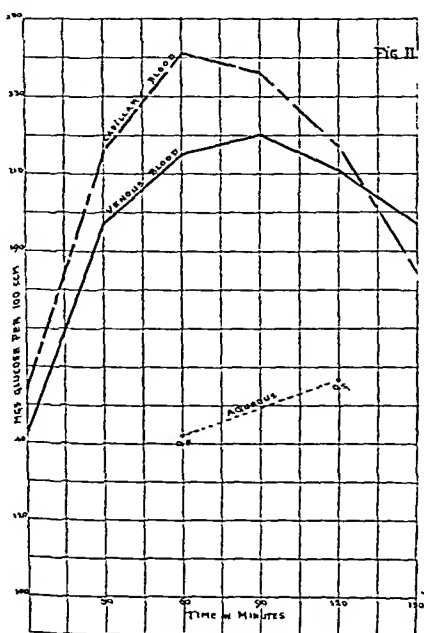


Fig. 234.—Composite curves of sugar tolerance tests on seven diabetics.

In the diabetic type the rise is relatively slower and of longer duration. It is therefore not so much the height to which the

of the regenerated aqueous and that of the primary aqueous humor of the other eye, obtained at nearly the same time, would be greater in cases of diabetes mellitus than in nondiabetics with normal sugar metabolism. However this was not found to be the case in a series of 5 diabetics and 5 nondiabetics on whom secondary paracentesis was performed during tolerance tests. With the exception of the last two cases on Table 3, to which we shall return later, no striking differences are observed in the ratios. The primary aqueous of the other eye was always taken within five minutes after the secondary paracentesis of the first eye. One hour or more was allowed to elapse between primary and secondary paracentesis of the same eye. Most of the cases showed a failure of rapid equilibration between the concentrations of glucose in the blood and the secondary aqueous. This could only be interpreted as evidence of decreased permeability of the tissue barrier which lies between the blood and the aqueous.

The greatest difference between the primary and secondary aqueous humor sugar concentrations you observe in the second case on Table 3, where the ratio of 1.13 exceeds that of the primary aqueous humor in the left eye, taken within five minutes.

Two Interesting Cases of Cataract and Diabetes.—In this group are 2 cases of exceptional interest. These are the last two cases on Table 3. The first of these cases (Fig. 236) is that of a man of fifty-two, with senile cataract in the left eye on which a preliminary iridectomy was performed two months previously. The other eye is normal except for a slight amber hue. Now compare the change in glucose concentration of the primary and secondary aqueous humor in the two eyes. In the "good" eye, the aqueous humor sugar rises above the blood sugar level in the regenerated aqueous humor. A higher peak in the blood sugar curve might have occurred between the two points of blood sugar analyses, and the aqueous humor glucose at that point may only approach the blood sugar concentration. Such a peak may also be postulated from the established rise in aqueous humor sugar concentration.

thirty minutes after the insulin injection, followed by a steep descent. This was a woman of forty-seven, with incipient

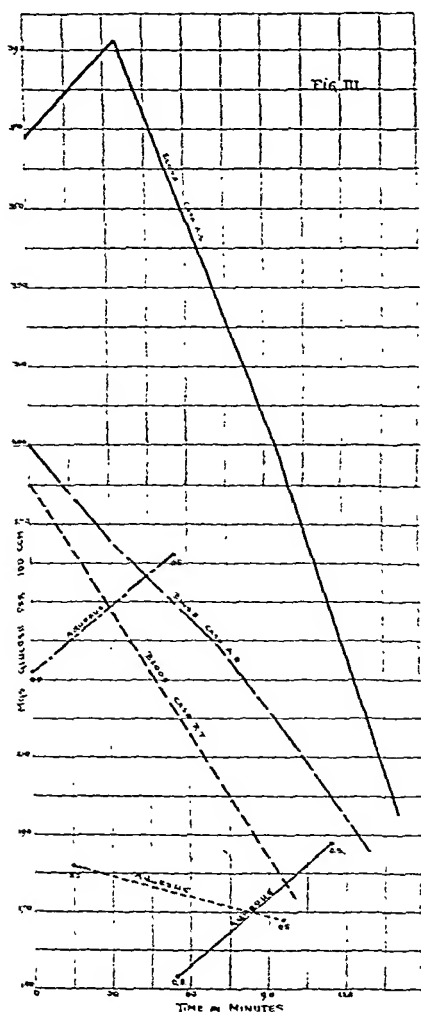


Fig. 235.—Changes in glucose concentrations in capillary blood and aqueous humor following insulin in three diabetics.

peripheral cataract. In the right eye many small hemorrhages and a cloudy vitreous. She was a moderately severe diabetic on a daily carbohydrate intake of 100 Gm. with 35 units of

ing the hyperglycemia, it lies at a low fasting level, 71 mg. below the point on the sugar curve. In the regenerated aqueous humor this has undergone a further drop to the low concentration of 76 mg. per 100 cc. In the good eye there is a normal or even slightly increased rate of diffusion of the glucose. In the cataractous eye there is practically sugar starvation, at least as compared with the condition of the other

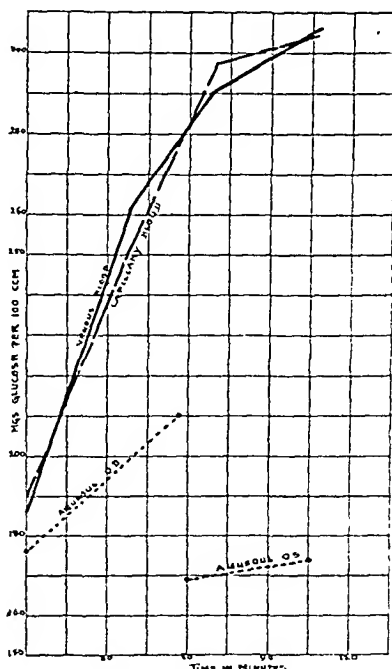


Fig. 237.—Comparison between the glucose concentrations of primary and secondary aqueous humor in a patient with double aphakia and discission in one eye during a sugar tolerance test with capillary and venous blood sugars.

eye. The other case (Fig. 237) is that of a woman of seventy-four, a diabetic with double aphakia. In the left eye cataract extraction was followed by discission. In this eye, therefore, the aqueous humor is in contact with the vitreous body. Now observe the difference in sugar concentration of the aqueous humor of the two eyes. In the right eye, in which the barrier between the aqueous and vitreous is intact, the primary

TABLE 3

Eye condition and complications.	Nature of test.	Ratio of aqueous humor sugar to blood sugar.			
		Primary R. E.	Secondary R. E.	Primary L. E.	Secondary L. E.
Lens haze, nuclear sclerosis. Diabetes mellitus (mild).....	Post food.	0.75	0.86	0.93	
Cort. cataract R. E. Incip. cataract L. E. Diabetes mellitus. Hypertension.....	Post food and insulin.	0.80	1.12	1.05	1.16
Acute glaucoma and iritis.....	Tolerance.	0.67	0.57		
Acute glaucoma and iritis.....	Tol. post breakfast.	0.49	0.51		
No eye condition. Mild diabetic acidosis.....	Post food and insulin.	0.84	0.83	0.81	
Senile cortical cataract. Arteriosclerosis.....	Post food.	0.88	0.94	0.93	
Incip. senile cataract. Mild hypertension.....	Post food.	0.73	0.75	0.78	0.90
Mature senile cataract.....	Tolerance.	0.81	0.57		
Senile cataract. Arteriosclerosis...	Post food.	0.60	0.70	0.66	
Unilateral senile cataract L. E.	Post food.	0.75	1.05	0.56	0.55
Double aphakia. Discission L. E. Diabetes mellitus.....	Tolerance.	0.95	0.77	0.61	0.57

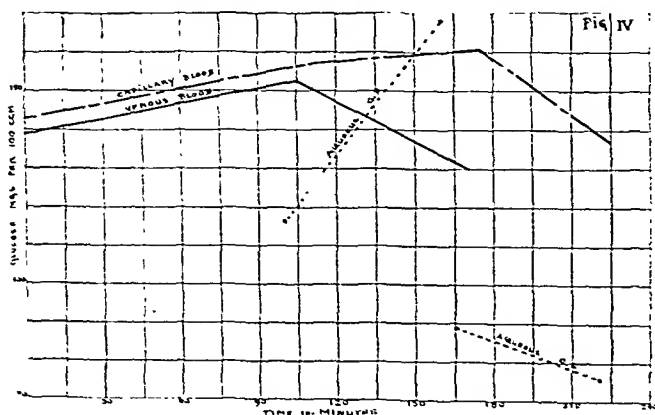


Fig. 236.—Comparison between the glucose concentrations in primary and secondary aqueous humor of normal and cataractous eyes of same patient after food intake with determinations of glucose concentrations in capillary and venous blood.

Now observe the aqueous humor glucose of the cataractous eye. Although the primary aqueous humor was obtained dur-

fasting condition. Following the ingestion of carbohydrate material and subsequent hyperglycemia, the sugar concentration of the aqueous humor also rises, but the rise lags behind that of the blood, extends into the period when the blood sugar diminishes, and is less pronounced than the glycemia. The height of the rise of the aqueous sugar depends more upon the duration of hyperglycemia than upon the height of the rise of the blood glucose. In cases of brief hyperglycemia there may be very little rise in the aqueous sugar. In patients with mild diabetes mellitus or in those elderly patients who showed a diabetic type curve in their sugar tolerance tests, there is no essential difference in this relationship between blood sugar and aqueous humor sugar, except that coincident with the more pronounced and enduring hyperglycemia, following ingestion of carbohydrate, the glucose concentration of the aqueous continues in its slow increase for a slightly longer period. The sugar concentrations of the regenerated aqueous humor did not show any striking differences from those of the primary aqueous of the other eye, taken within a five-minute interval, except in those cases in which there was a marked difference in pathology in the two eyes.

The rise in sugar concentration of the aqueous humor in diabetes mellitus does not seem to be the etiologic factor for the greater incidence of cataract in this disease. Other pathologic changes, such as the acidosis, resulting from disturbances in fat metabolism and the decreased permeability of the tissues and abnormal water metabolism in this disease may play a more important rôle. One of our most important findings was the evidence of decreased permeability of the tissue barrier between the blood and the aqueous in these cases of cataract and diabetes.

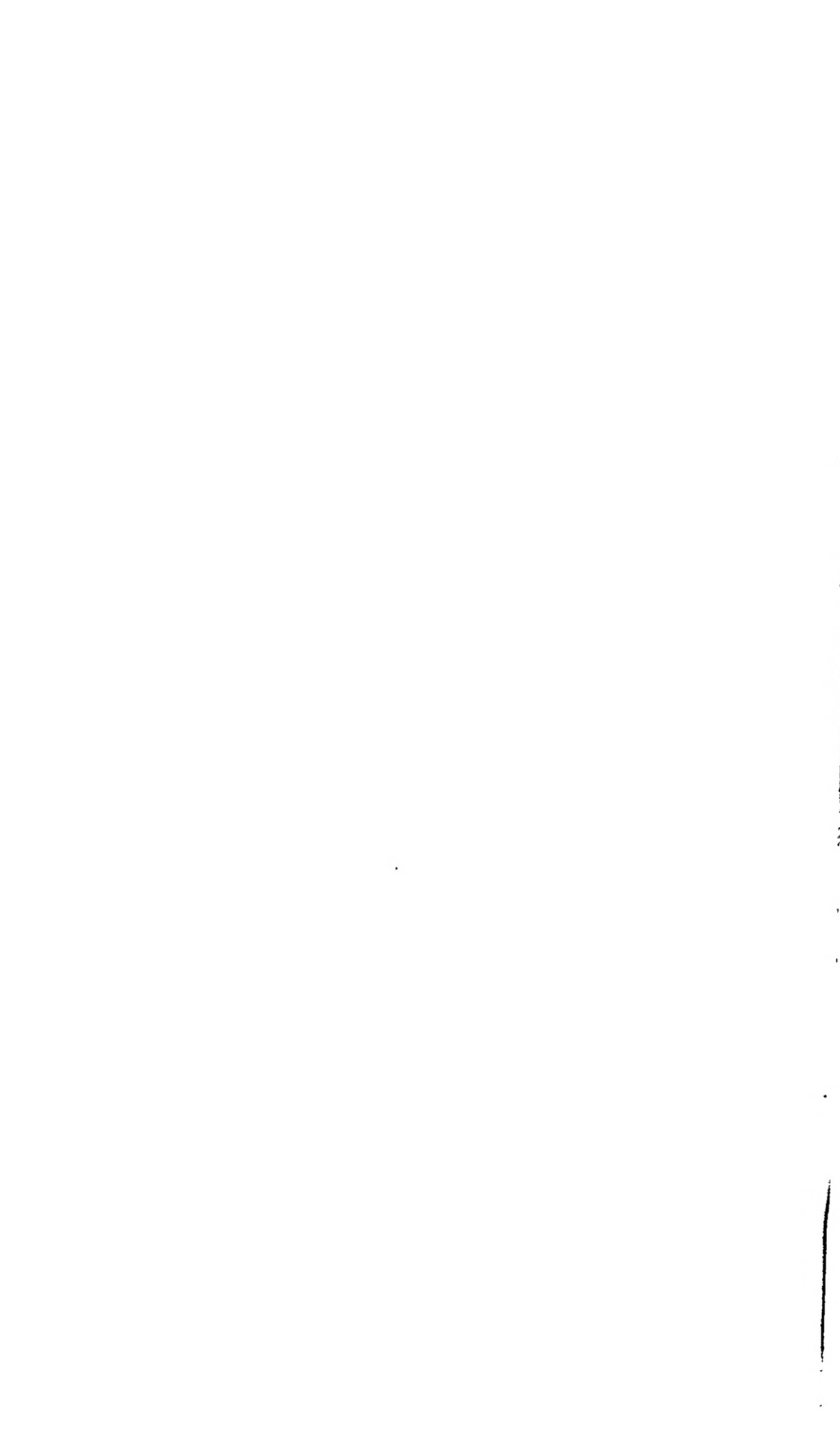
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aqueous, taken in a fasting condition, closely approaches the blood in its sugar concentration. The secondary aqueous taken fifty-five minutes after the ingestion of 32 Gm. of glucose in 10 per cent solution has risen, but far less so than the blood sugar curve. Now observe what happened in the other eye. Although the primary aqueous was taken sixty minutes after the ingestion of the glucose drink, at a time when the blood sugar curve had reached a height of 280 mg., its sugar concentration lies below that determined for the primary aqueous of the other eye in a fasting condition. Although the rise in blood sugar concentration continues into the second hour, the regenerated aqueous humor of this eye shows only a minimal rise, less than 3 per cent. In this eye, with its lack of barrier between vitreous and aqueous, a factor is introduced which is normally lacking, that is the consumption of glucose by the retina. The sugar concentration of the vitreous has been shown to be materially less than that of the aqueous or lens. Adler⁵ has shown that the posterior layers of the vitreous, in contact with the retina, have a lower sugar concentration than the anterior portion and he attributes this to the marked glycolytic power of the retina.

Carbohydrate Tolerance of Patients with Senile Cataract.—We have shown that the carbohydrate tolerance of patients with senile cataract is frequently slightly decreased. This one would expect from a consideration of the age group to which these patients usually belong. Old age is one of the most important physiologic factors influencing sugar tolerance. In a study of senile cataract patients by means of sugar tolerance and sugar depletion (insulin reaction) tests, we found the hyperglycemia of elderly people with cataract to be simply another expression of the diminished functions of old age.⁴

Summary and Conclusions.—We may state that the concentration of glucose in the aqueous humor is less than in the capillary or the venous blood. Of the seventy-five patients studied, sixty-five had senile cataract and thirty-five were also diabetics. The aqueous humor glucose concentration approaches the blood sugar concentration most closely in the



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4. Kirby, D. B., and Wiener, R. V. E.: The Relation of Disturbances of Carbohydrate Metabolism to Cataract, *Trans. Amer. Acad. Ophthal. and Otolaryng.*, 1932.
5. Adler, F. H.: Sugar Content of Ocular Fluids and Glycolytic Activity of Tissues of the Eye, *Trans. Amer. Ophthal. Soc.*, 1930.

duodenal ulcer is more frequently located on the anterior wall than is gastric ulcer. It is this factor, *i. e.*, anterior wall, that is the significant element in frequency.

The area of perforation is oval or round. Its size varies with the individual case. When there are infarcted areas in the region of the ulcer, especially in the stomach, the perforation may be very large. In one case that we observed it was so extensive as to permit, at postmortem, the insertion of a hand. As a rule, however, the perforated area is no larger than a pea or a hazel nut, often not that large, especially if the ulcer is in the duodenum.

PERFORATION WITH ACUTE SYMPTOMS

The perforation followed by acute symptoms generally occurs when the stomach is full, allowing the gastric contents to escape into the abdomen. It may happen without warning or, as is more often the case, it may be preceded by several hours or days of upper abdominal distress, especially by a feeling of bloatedness. Moynihan said once, "If one always remembered that a sudden aggravation of ulcer symptoms may indicate impending perforation, there would be fewer perforations."

At the moment of perforation, there is felt a sudden, sharp pain which is variously described. Some patients refer to it as being like the "stab of a knife." Juillard has reported a case where the patient said he felt a painful sensation as of a "jet of burning liquid poured from a cruet into the bowels." This pain is so severe that it causes the patient to sink down in utter collapse, remaining for half an hour or more in a motionless semistupor, moaning with pain. The face is drawn, the eyes are sunken. It is truly the *facies hippocratica*. The entire body is covered with cold, clammy perspiration. The fingers are cyanotic. The pulse is rapid and feeble. The temperature, as a rule, is subnormal. Breathing is entirely costal. The abdomen is generally rigid, not from early peritonitis but due to muscular resistance. The slightest touch upon the abdomen enhances the pain. If the abdomen is

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PERFORATED PEPTIC ULCER

A PERFORATED ulcer is usually classified, according to severity and duration of the symptoms, as acute, subacute, or chronic. In reality, every perforation is acute in onset, although not all give rise to acute symptoms. Some give rise to subacute and others to chronic symptoms.

Before the era of x-ray diagnosis of gastro-intestinal lesions, when frequency was calculated on the basis of operative and postmortem findings, the type of perforation thought to occur most often was that with acute symptoms. Today, however, it is known that the greatest number of cases give rise to subacute or chronic symptoms of varying duration.

The site of the ulcer is an important factor in frequency. An ulcer is most apt to perforate when it is situated in the lower end of the esophagus; such an ulcer may perforate into the mediastinum with resulting suppurative mediastinitis or suppurative pneumonitis; into the pleura of the lung with ensuing empyema or a pyopneumothorax; or into the pericardium causing purulent pericarditis. These grave conditions follow perforation so swiftly that a diagnosis is seldom made during life. In a few cases, however, the perforation heals spontaneously and the resultant empyema or mediastinal abscess is successfully treated.

At one time, it was believed that an ulcer in the duodenum was more likely to perforate than one in the stomach. Indeed, pathologists said formerly that the gravity of duodenal ulcer lay chiefly in the risk of perforation. It is true that more duodenal than gastric ulcers perforate, but this is because the

areas of suppuration, followed by pyopneumothorax, form in the subphrenic spaces, necessitating a secondary operation. Between the operation for perforated ulcer and the development of a complication, there may be a period of repose, lulling one into a false belief that all is well. A case of this nature is that of a man of some forty years who had suffered for many years from such vague gastric symptoms that, in connection with his exceedingly neurotic behavior, they were adjudged signs of functional derangement. Four days prior to the patient's admission to Beth Israel Hospital, he developed acute abdominal pains with distention. Even these violent symptoms were not taken seriously by the physician. It was the patient himself who insisted upon hospitalization. The roentgen examination revealed free air under the right dome of the diaphragm. The patient was operated by Dr. De Witt Stetten in the afternoon of the day of admission, and the findings confirmed the preoperative diagnosis of a perforated duodenal ulcer. There ensued two weeks of very favorable reaction on the part of the patient, then the symptoms of a subphrenic abscess presented themselves. The patient was reoperated. There again followed a period of encouraging convalescence finally interrupted by a pyopneumothorax for which the patient underwent a third operation. After that, the patient recovered completely and has continued well.

DIFFERENTIAL DIAGNOSIS BETWEEN PERFORATED ULCER WITH ACUTE SYMPTOMS AND OTHER INTRA- AND EXTRA- ABDOMINAL CONDITIONS

Acute Appendicitis.—Acute appendicitis may resemble perforated ulcer, and vice versa. It is not surprising that an acute attack of appendicitis with diffuse abdominal symptoms often simulates perforation of a peptic ulcer. This is especially true when the appendix is situated very high in the abdomen, under the liver, or when it is located in its usual position, but, being chronically diseased, has given rise to a history of reflex gastric symptoms.

With regard to the perforation that is erroneously mis-

pendulous, there may be relaxation instead of rigidity of the abdominal walls so that before drawing a conclusion one must be careful to ascertain that the relaxation is not the effect of morphine. Tympany is not present in the early stage of collapse; instead, there may be dulness on percussion.

Within half an hour or so, the temperature begins to rise and local signs of peritonitis make their appearance. The manifestations of collapse diminish, except that the pulse continues to be feeble and rapid and the blood pressure low. The abdomen is distended. Tympany is now present, especially over the liver. By careful auscultation in the region of the liver, as pointed out by Gibson,¹ one may detect the escape of air from the duodenum, a significant finding. Auscultation over the heart reveals a sharp first sound; sometimes a sharp first sound followed by a very short second sound. The sharp first sound is diffuse over the chest; in fact, it may be heard over the entire abdomen. Examination of the blood nearly always reveals leukocytosis, and, unfailingly, an increase in staff cells.

Roentgen examination generally establishes the diagnosis. The patient is examined fluoroscopically and a flat film is taken. No matter how soon after perforation the examination is made, free air is almost invariably visible. When the ulcer is on the lesser curvature of the stomach, there is free air between the left dome of the diaphragm and the spleen. When a duodenal ulcer has perforated, the free air appears under both domes of the diaphragm.

Recovery depends upon how soon after perforation the patient is operated. In those cases fortunate enough to have immediate surgical attention, although the ulcer is not excised and not even a gastro-enterostomy is performed but the perforated area is merely sutured, one finds the greatest number of recoveries. If operated within six to twelve hours of the perforation, about 80 per cent recover; if within twelve to twenty-four hours, 50 per cent; after this, between 5 and 10 per cent.

Convalescence is always protracted. Very often localized

foration and, during the period of pain, respiration is chiefly costal.

Acute Hemorrhagic Pancreatitis.—Both perforation and pancreatitis begin with acute pain in the upper abdomen and manifestations of varying degrees of shock. The shock disappears more rapidly in the former than in the latter condition. As fat necrosis progresses in acute hemorrhagic pancreatitis, shock returns, with resulting peritonitis that is impossible of differentiation from perforated ulcer. Prior to the occurrence of peritonitis, however, there are certain typical differential features. Although shock is present in acute pancreatitis, the face is flushed and cyanotic, in contrast to the *facies hippocratica* of perforation. The upper abdomen is distended and excruciatingly painful to touch, the lower abdomen is not distended and is not very tender on palpation. Liver dullness is not obliterated. The abdominal reflexes are seldom absent in the first few hours; if absent, they are missing only over the lower abdomen. These reflexes are normally absent in obese women or those who have given birth to many children, a point one must bear in mind, since acute pancreatitis occurs predominantly in women, especially of this type. The pain radiates to the chest, more specifically to the left shoulder, which is tender to touch and motion to a degree simulating synovitis and bursitis. In the majority of cases, there is a sensitive pressure point over the left costovertebral region, from the ninth dorsal to the first or second lumbar vertebra. Examination of the urine not infrequently shows the presence of sugar, a reliable guide to diagnosis. In all cases the urine and serum should be examined for diastase, as advocated by Wohlgemuth;² when the diastase is increased acute pancreatitis is a reasonable diagnosis. Such a diagnosis is strengthened by a history of frequent attacks of biliary colic because acute pancreatitis very often occurs in women who have been afflicted with gallbladder disease for many years.

Not all cases of acute hemorrhagic pancreatitis have an onset of severe pain accompanied by collapse. Sometimes the symptoms are not violent enough even to keep the patient

taken for acute appendicitis, Dieulefoy reported that of 49 cases of perforated ulcer, 19 came to operation with a diagnosis of acute appendicitis. He thought that the error in diagnosis is due to the fact that when a duodenal ulcer perforates, the fluid released from the duodenum goes, first, to the upper surface of the transverse mesocolon, thence downward to the hepatic flexure, next to the upper side of the ascending colon, and finally, into the pelvis whence it spreads over the ileocecal region, and, in fact, through the entire lower abdomen.

But whether appendicitis simulates perforation, or perforation acute appendicitis, there are several distinguishing features to enable one, generally, to decide the actual nature of the illness. The exception is the case where an inflamed appendix is located very high under the liver. Here, the severe pain and associated spasm of the diaphragm may make differential diagnosis impossible for several hours. Early operation is essential in each condition, however. So the welfare of the patient is not jeopardized, if the differential diagnosis is not established. Should the operation have to be delayed, the progress of the disease, of course, will reveal its nature. If the cause is a diseased appendix high under the liver, peritonitis is usually absent, the pain becomes localized in the right upper abdomen, and there is rigidity in this region. Moderate icterus or yellowish discoloration of the sclera, and bile pigments in the urine may occur, resembling biliary duct disease.

The outstanding difference between the usual case of acute appendicitis and perforation is the mode of onset. The former nearly always begins with severe pain, followed immediately by vomiting; in the latter condition, there is no vomiting except prior to the onset of pain, and even then vomiting is rare. Other distinguishing features are: In appendicitis, rigidity is confined to the right side of the abdomen whereas in perforation the entire abdomen is rigid even before the stage of peritonitis; the pain of appendicitis is not as severe or as persistent as in perforation; the diaphragm is fixed in per-

to touch, the abdomen may be easily palpated. In the course of palpation, peristaltic unrest is frequently noted, being visible in thin individuals.

Fluoroscopy and flat films are of great assistance in arriving at a diagnosis. One usually sees immensely dilated small intestine. There is rarely any free air between the diaphragm, liver or spleen. Occasionally coils of small intestine containing air and fluid lodge between the right dome of the diaphragm and the liver, or between the left dome and the spleen, simulating free air.

An examination of the blood is of value. Haden and Orr³ have shown that in small intestinal obstruction, especially when situated high, the chlorides are diminished whereas urea and noncoagulable nitrogen are increased. There is no leukocytosis. The urine often contains a great deal of albumin and casts which has led some observers to consider that renal damage is responsible for the high nitrogen figures in the blood. This is not acceptable, however, because if there were renal damage the chlorides in the blood would increase and this is not the case. There is definitely an extrarenal azotemia or hypochlorazotemia.

Biliary Colic.—Although this condition occasionally so nearly resembles a perforated ulcer as to make diagnosis most difficult, especially during the first hour of acute symptoms when the patient is in collapse, there are nevertheless points of differentiation. Outstanding is the fact that the patient is extremely restless, tossing about in bed. Breathing is entirely thoracic and, owing to diaphragmatic spasm, may be so harrowing as to overshadow the symptom of pain. Expulsion of air or vomitus affords temporary relief. The pain usually radiates to the chest, particularly to the right side, and to the right shoulder; if radiation is absent, marked pressure tenderness over the right shoulder clavicular joint (Westphal sign) is almost invariably present. During the stage of collapse, the pulse is neither as rapid nor as feeble as in perforation. Indeed, it may be as slow as in syncope. Although the upper abdomen, which is very tender to touch, seems rigid, actually

in bed. He may call to see the physician in his office. Two cases of this kind recently came to us. One was a young man of twenty-three years with a history of pyrosis and hunger pain of several years' duration, strongly suggesting peptic ulcer. One midnight he had an attack of severe pain. In the morning he came to the office with pain and slight rigidity in the upper abdomen. The pain radiated to the back but there was no left shoulder pain and no pain in the left costovertebral angle. We diagnosed the case as one of slow perforation of a peptic ulcer. The patient was admitted to Israel Zion Hospital and was operated by Dr. Wm. Linder. The stomach and duodenum were entirely normal, and the cause of the illness was found to be hemorrhagic pancreatitis. He recovered from the operation.

The second patient was a woman who came in with pain in the upper abdomen. She vomited repeatedly, but had no symptoms of shock or collapse. The previous clinical history did not reveal anything very definite. Diagnosis wavered between gallstones and peptic ulcer. The fact that she was obese and that some of the attacks appeared during her pregnancies and lactation led us to diagnose the condition as gallstones. There were no symptoms or signs to arouse a suspicion of pancreatitis. At operation, gallstones were found in the gallbladder, but they were dormant, and the attack was found to have been due to acute hemorrhagic pancreatitis.

High Intestinal Obstruction.—The characteristic manifestations of this condition which sometimes so closely simulates a perforated ulcer as to render diagnosis exceedingly difficult, are the following: The sudden onset of pain is usually followed quickly by vomiting out of proportion to the severity of the pain; the first vomitus consists of gastric contents, succeeded by vomitus with an odor as of decomposition, this later vomitus coming actually from the small intestines; the facial expression is strained and pinched but it is not *faciès hippocratica*; the temperature is seldom elevated but is apt to be subnormal; the pulse is rapid; and the blood pressure is not as low as in perforation. Although distended and tender

removed by surgical procedure. The patient completely recovered. In retrospect, we realize that there was more vomiting than would have been the case in perforation and that the abdomen, although distended and painful, was not very rigid. Moreover, the abdominal reflexes were obtainable only by repeated effort, and the abdominal breathing was not as restricted as in most cases of perforation. We remarked about these findings at the time but they were not sufficiently clear cut to guide us to the right diagnosis, especially as the symptoms of perforation need not be classical.

Mesenteric Thrombosis.—This condition generally occurs during the course of malignant hypertension or advanced secondary contracted kidney, or an ulcerative arteriosclerotic aorta, where there is no conflict in diagnosis. Occasionally, however, it happens in an affection such as myocardial weakness secondary to coronary artery disease where there is neither high blood pressure nor specific renal signs to furnish a trustworthy clue. The onset of mesenteric thrombosis, be it venous or arterial, is characterized by excruciating pain. When the thrombus is in a vein, this pain is persistent; the patient moans incessantly, even during the stage of peritonitis in contradistinction to the euphoria that prevails in peritonitis due to perforated ulcer. The bowel evacuations are scant, the small amount of feces being mixed with bright red blood. In the absence of blood in the stool, blood is usually detected on the finger if a digital examination of the rectum is made. When a thrombus lodges in an artery, the ischemia of the intestines supplied by the artery causes unbearable pain. As necrosis sets in, the pain diminishes and the unmistakable symptoms of intoxication appear, namely, the pulse is very rapid, the patient becomes drowsy, and death is almost always immediately preceded by convulsions. At no time is there blood in the stool. In rare fortunate cases, canalization of the thrombus occurs during the stage of ischemia whereupon circulation is reestablished, all symptoms disappear, and the patient recovers.

Intra-abdominal or Diaphragmatic Hernia.—An intra-

it is not. Morphine will completely relax it. On the other hand, there is rigidity of the upper, and sometimes of the entire abdomen where the gallbladder infection has progressed rapidly to a gangrenous state. If the common duct is occluded, one almost always finds an increased icteric index and an increase in the direct bilirubin in the blood.

Facies hippocratica is present in some cases of biliary colic. When it is, and there is also an elevated temperature, it may be impossible to differentiate between it and perforated ulcer.

Renal Colic.—We have encountered one case where, had there been no x-ray examination with ureteral catheterization, differential diagnosis between renal colic and perforated ulcer would have been impossible. It is rare for the features of these two diseases to be so nearly identical that pressure tenderness over the affected kidney will not reveal the cause of the attack but, occasionally, such similarity does exist. In renal colic, there is usually pressure tenderness over the testicle on the affected side, perhaps over both testicles. Occasionally, there is hyperesthesia of the scrotum, or, in the female, of the labia majora. The urine nearly always contains red blood cells. Our patient with renal colic had long suffered from hyperacidity, hypersecretion, and other forms of gastric distress. When he began to experience piercing abdominal pain with acute abdominal distention, the immediate inclination was to diagnose perforated ulcer, especially in view of an absence of all urinary findings except diminished output, a phenomenon that is, also, an accompaniment of many acute abdominal affections. Against perforation, however, was the absence of free air under the dome of the diaphragm, while in favor of renal colic was roentgen evidence of a stone (in a flat film) which, unfortunately, could not be localized in either the pelvis of the kidney or in the upper ureter until catheterization showed the obstruction in the upper right ureter. The symptoms continued to be so much those of perforation, however, that despite positive evidence to the contrary, we doubted the accuracy of a diagnosis of renal colic until the stone was

with respiration; deep palpation of the abdomen is not painful, but may afford relief; and the abdominal reflexes, although superficial, are almost invariably obtainable, and are, occasionally, hyperactive. There is usually an elevation of temperature. Fluoroscopic examination is helpful. No matter how early in its course the case of pleurisy is seen, there is restricted mobility of both domes of the diaphragm, the dome on the affected side being much the higher of the two. There is no free air between the diaphragm and the abdominal viscera.

Coronary Thrombosis.—When coronary thrombosis is followed within a few hours by cardiac infarction with the symptoms localizing in the upper abdomen instead of in the chest, it is not unusual for a mistaken diagnosis of perforation to be made. In earlier days, when the symptom complex of coronary thrombosis was less well known than it is today, many such patients went to the operating table as a case of perforated ulcer. As soon as definite manifestations of cardiac disease present themselves diagnosis is clear, but in the six to twelve hour period between the initial onset and the appearance of the absolute cardiac picture, diagnosis is difficult. Outstanding differential features of coronary thrombosis are: The complexion, in the early stage of collapse, is ashen gray, turning to sallow or to a flush, if the temperature is elevated; at no time is there *facies hippocratica*; vomiting often occurs in the first stage, affording relief, followed by nausea and no vomiting; the tongue is never parched; breathing is both thoracic and abdominal; the pulse may be extremely slow due to heart block or it may be rapid with embryonic heart sounds. Occasionally there is actual paroxysmal tachycardia of the sinus, auricular or ventricular type. Should the abdomen be distended, as it sometimes is, pressure tenderness is present, though not severe, being confined to the upper abdomen and mainly to the hepatic region. Audible pericardial friction over the precordium is an absolute sign, of course, of coronary thrombosis. An electrocardiogram should be made as soon as possible, in all cases. In coronary occlusion with

abdominal hernia, such as invagination of an internal loop of omentum into one of the internal rings, for instance the foramen of Winslow, may occur with such violent abdominal pain, followed by collapse and rigid abdominal distention, as to simulate the perforation of an ulcer so closely that clinical differentiation is impossible. Diagnosis is sometimes aided (if the small intestines invaginate an internal ring) by the symptom of profuse vomiting and by the detection by rectal examination of a part of the invaginated loop of intestine. As in other forms of intestinal obstruction, there is a diminution of chlorides and an increase of nonprotein nitrogen in the blood. The urine is scanty and contains albumin and casts.

Diaphragmatic hernia sets in with extreme pain in the upper abdomen radiating to the left side of the chest, especially if the hernia causes volvulus of the stomach. The chest pain is almost equal in intensity to that in the abdomen. The pain is accompanied by vomiting and collapse. Toxic symptoms may be as outspoken as the abdominal and thoracic symptoms. There is marked difficulty in breathing with cyanosis, suggesting the possibility of a perforation of the lung with a resulting pneumothorax. In most cases of invaginated diaphragmatic hernia, whether simulating a perforation or giving rise to symptoms of a pneumothorax, the diagnosis is suggested by the fact that within two or three hours of onset the heart is entirely displaced to the right and there is definite succussion in the left chest, as in hydropneumothorax. Because hydropneumothorax following pneumothorax does not develop within a few hours, the presence of succussion should establish a diagnosis of invaginated diaphragmatic hernia. Diagnosis is extremely important at this stage because early operation can save the life of the patient.

Pleurisy.—During the early stages of pleurisy, especially of diaphragmatic pleurisy and of pleurisy of the lower lobe of the right lung, symptoms may be confined to the upper abdomen, the pain being as severe as in perforated ulcer. The differentiating points are: There is restricted thoracic but visible abdominal breathing, the alae nasi dilate actively

connection with trauma to the lower dorsal and upper spinal nerves.

Paralytic Ileus.—In this lesion, abdominal distention may very closely simulate peritonitis due to perforation, but in paralytic ileus there is *borborygmi*. It is sometimes although not often necessary to anesthetize the patient in order to produce sufficient relaxation of the abdomen to establish diagnosis. Fluoroscopical examination generally reveals restriction but not elevation of both domes of the diaphragm. If a flat film is made, gas is seen throughout the colon and possibly in the small intestine. There is no free air between the domes of the diaphragm and the spleen or liver.

PERFORATION WITH SUBACUTE SYMPTOMS

When a small perforation occurs, the initial symptoms may be so mild as to escape attention so that the patient does not consult a physician until some condition develops that is a result of the perforation. Very often there is nothing in the history to indicate a perforation.

Such a perforation may be followed at once or within a few days by reactive inflammation or by suppuration. If there is reactive inflammation, after the inflammatory changes subside chronic productive changes take place, the clinical significance of which will be discussed later. Very often, however, the inflammatory changes are followed by suppuration.

As perforation most often occurs on the posterior wall of the stomach or duodenum, the suppurative process generally settles in one of the four right subphrenic spaces, that is: (1) between the liver and diaphragm; (2) below the liver, in the gastrohepatic region; (3) in the lesser sac of the peritoneum, (4) in the retroperitoneal region behind the duodenum, often in conjunction with an abscess in right or left hypochondrium.

The systemic symptoms are often out of proportion to the local symptoms. This is especially true if the suppuration does not localize at once.

Occasionally the suppuration settles between the upper surface of the spleen and the diaphragm. When inflammation

rupture of the intraventricular septum pain in the upper abdomen is so pronounced as to focus one's attention to that region. The rapid development of a loud harsh murmur over the precordium, however, soon enables one to make the correct diagnosis.

Trauma to the Lower Dorsal or Upper Lumbar Spinal Nerves.—From time to time one sees an injury in this region causing severe abdominal pain and producing marked abdominal rigidity simulating peritonitis. Should the injured individual happen earlier to have had symptoms of peptic ulcer, it is natural for one to think that the sudden acute symptoms have arisen from a perforation. Diagnosis is usually established by the following findings: The collapse manifestations are much more transitory than in perforation; vomiting is more pronounced; breathing is abdominal, never thoracic; and there is often retention of urine with marked distention of the bladder, adding to the patient's distress until reduced by catheterization. Superficial palpation of the abdomen may be painful but one can gradually so overcome this resistance as to be able to palpate deeply. The slightest motion of the body, however, will produce acute distress. The spinal vertebrae in the injured region as well as the spinous processes, and even both right and left intercostal spaces, are exceedingly tender to palpation. The abdominal reflexes are exaggerated or normal, never absent. The paravertebral injection of $\frac{1}{2}$ to 1 per cent novocaine in the most sensitive region will occasionally assist in the diagnosis by entirely relieving the pain at least temporarily if it is due to spinal nerve injury.

Encephalitis.—The statements about spinal nerve trauma are occasionally true of encephalitis when there is radiculitis of the tenth to the twelfth dorsal nerve roots. During the encephalitic epidemics of 1918 and 1919, many patients were operated in the belief that an ulcer had perforated, especially where shock and collapse manifestations were marked. Perhaps such errors are excusable in the stress of an epidemic, but as a rule ordinary care in the examination of a patient will reveal the distinctive, differentiating features enumerated in

becomes less acute but more persistent. This persistent gnawing pain is most marked in the lower chest both anteriorly and posteriorly and in the hypochondrium. The temperature which was somewhat elevated during the early stage—rising to 102° and 103° F.—becomes subfebrile in type, that is, 99° F. in the morning, 101° F. in the afternoon. The thoracic symptoms are far more outspoken than the abdominal symptoms. Breathing is painful, particularly on inspiration. There is frequent cough due to compression of the lung and to irritation of the phrenic nerve. The cough is more troublesome at night than during the day. Lying on the affected side causes discomfort.

The patient loses weight and begins to show signs of anemia, although the hemoglobin and the red blood cells may be only moderately reduced in number. Leukocytosis is not present, as a rule; at most, the leukocyte count is moderately elevated, but there is a definite tendency to an increase in polymorphonuclears.

Physical examination of the chest at this stage often shows flatness, diminished or almost entirely absent breathing over the base of the lung and markedly restricted mobility, indicating the existence of fluid in the chest. Very often this fluid is accused as the cause of the affection. In reality, however, it is a sympathetic effusion which, in the vast number of cases, is a pure serous fluid. A mistake in diagnosis of primary fluid in the chest is avoidable if one finds that, in contradistinction to effusion in the chest where dulness or flatness is present in the axilla, there is flatness confined to the posterior aspect of the lower chest. Moreover, in primary effusion the fluid on the left side obliterates Traube's space and pushes the heart to the right side, or, if present on the right side, pushes the liver down considerably, whereas if there is sympathetic fluid no displacement of the organs takes place. If there is pain in the presence of fluid, primary effusion is ruled out. One must bear in mind, however, that this finding may be present when there is a mediastinal tumor or a tumor of the bronchus or lungs.

plus suppuration does settle in this region, or between the upper surface of the liver and the diaphragm, local symptoms appear early but may be so vague in nature that the condition is often erroneously diagnosed as an intrathoracic pathologic lesion.

Abscess Between the Superior Surface of the Liver and the Right Dome of the Diaphragm.—The most frequent location of a subphrenic abscess is between the superior surface of the liver and the right dome of the diaphragm. Even before active suppuration has set in there are symptoms referable to the thorax on the affected side and objective signs of disturbance in the upper abdomen. Chief among these symptoms is pain over the chest on the right side, which is aggravated on breathing, in this respect arousing a suspicion of pleurisy. However, the patient does not experience the "stitch in the side" or the catch of the breath on deep breathing, particularly on inspiration, that is characteristic of pleurisy. What the patient has is actual neuralgic pain on breathing. This pain, over the lower ribs in the axillary region and also posteriorly, is aggravated by pressure from without, differing in this respect, also, from the pain of pleurisy. In the early stage, there is pain in the right hypochondrium as well. There is usually diminished breathing over the lower chest and occasionally there are a few crepitant râles which disappear on coughing, indicating atelectasis of the lower lobe of the lung and often mistaken for pleuritic friction or real infection of the lung. If an x-ray examination is made at this stage, one sees the right dome of the diaphragm moderately elevated and its mobility restricted, entirely out of proportion to early pleurisy or mild infection of the lower lobe. Paradoxical movement of the diaphragm is not present at this stage, but when the patient is made to cough or exhale forcibly the movement of the dome of the diaphragm on the right side is markedly affected while that on the other, normal side is freely upward. Mobility of the lower chest is restricted, demonstrable both to inspection and palpation.

As the suppurative process becomes localized the pain

admitted to Beth Israel Hospital. She entered with a diagnosis of unresolved right-sided pneumonia. Physical examination revealed dulness and crepitant râles at the base of the right lung, with restricted mobility of the right lower chest. The pain over the right side of the chest as well as that in the right hypochondrium was aggravated by deep respiration. This made us feel that we were not dealing with an unresolved pneumonia or pleurisy, but rather with subdiaphragmatic pathology. Fluoroscopic examination showed the right dome of the diaphragm to be considerably elevated and its mobility restricted, but there was no paradoxical movement. The temperature was moderately elevated (101° F. in the afternoon) and the blood count was within normal limits. In the course of a week, during which the symptoms did not abate, we became convinced that we were dealing with a subdiaphragmatic abscess. The surgeon, however, could not agree that this was the case and so the patient went home. Four weeks later we were summoned to her house, and now a mass was distinctly palpable in the right hypochondrium. We learned that the patient had had several chills during the previous week and that the pain had varied in severity. There was increased flatness over the base of the right lung. We advised her to return to the hospital but she did not do so for a week when she was brought in, in collapse. Physical examination revealed a pyopneumothorax. The palpable mass was still present. A needle was introduced directly into the mass and a large quantity of pus, mixed with bile, was obtained, proving that the abscess had perforated into the liver. Pus was obtained, also, from above the diaphragm. The patient could not be operated, owing to shock. She did not rally. Postmortem examination showed a pyopneumothorax due to subphrenic abscess plus perforation of the abscess into the liver.

Suppuration in the Gastrohepatic Region Below the Liver.—Here, too, the systemic symptoms are very marked in the beginning, consisting of chills followed by elevation of temperature and an absolute loss of appetite. The patient complains of pain in the right hypochondrium and there is

A sign of great value is the presence of three percussion zones, extending downward from the eighth intercostal space. The uppermost of these three zones is a region of tympany due to air in the upper layer of the abscess, and its breadth is approximately that of two fingers; the middle zone, consisting of three to four fingerbreadths of dulness, is caused by the abscess itself; the third zone is another region of tympany caused by distention of the colon. This is not a leading sign in left-sided abscess because of the resonance normally present over Traube's space.

x-Ray examination shows definite evidence of fluid in the chest. The dome of the diaphragm on account of this fluid is obliterated but the costophrenic angle is never as obliterated as it is when there is free fluid due to pleurisy.

In the advanced stage one may sometimes feel a palpable mass, sometimes simulating a large liver or pushing the liver down so as to awaken the suspicion of a liver abscess. In most cases where the abscess has lasted a long time, there is moderate suppuration of the liver adjoining the abscess.

Subphrenic abscess in this region if undiagnosed may go on to produce the following complications:

The abscess may break through into a neighboring organ, for instance into the liver and cause a liver abscess, or into the chest and cause a pyopneumothorax; or it may break through into some other neighboring organ, as, for instance, posteriorly to the pancreas. Sometimes the suppuration irritates the tail of the pancreas and leads to inflammation of the tail of the pancreas with cyst formation and at times to actual suppuration, affecting the islands of Langerhans to such an extent as to cause a severe degree of hypoglycemia.

Very rarely the suppurative process breaks through into the peritoneum to cause peritonitis, or it may break through into the intestines, the pus emptying through the intestines.

Occasionally such an abscess breaks through simultaneously into the liver and lung. We saw just such a case recently. The patient was a woman of sixty-five years who gave a vague history of abdominal pain starting four years before she was

symptoms and signs, the symptoms of infection are usually present.

Abscess in the Retroperitoneal Region Behind the Duodenum, Often in Conjunction with an Abscess in the Right or Left Hypochondrium.—When suppuration takes place in the retroperitoneal region behind the duodenum, the systemic symptoms are usually the following: Chills, followed by elevation of temperature, leukocytosis with an increase in polymorphonuclears and quite frequently a shift to the left of the polymorphonuclears. The patient complains of distress in the upper abdomen, but only after suppuration has developed to a considerable extent does the pain in the upper abdomen become marked. It is accompanied by resistance in the upper abdomen. There is often severe pain, too, in the lower dorsal and upper lumbar regions so that motion of the spine is exceedingly painful. Pressure of the abscess on the duodenum very often causes nausea and vomiting so that the patient can partake of little food. At practically no time can the abscess be palpated and at no time does it cause any reaction in the lower chest unless the suppurative process spreads into the right subphrenic space above the liver. The complication of such an abscess is that it may rupture into the small intestine and from there into the abdominal cavity, causing general peritonitis. Such an abscess may travel down behind the kidney, in which case it simulates a perinephritic abscess and even at operation one may not be able to decide definitely whether the abscess started as a perinephritic abscess or as a subphrenic abscess.

Left Subphrenic Abscess: Between the Spleen and Diaphragm.—Occasionally as a result of perforation of an ulcer there is a subphrenic abscess on the left side. All the symptoms are those of subphrenic abscess between the liver and diaphragm, except that they are on the left side and not the right. In some cases, the abscess gives rise to a definitely palpable mass, which may simulate enlargement of the spleen and lead to the not unusual erroneous diagnosis of splenomegalic disease or splenomegalic anemia.

resistance over the entire hepatic region. In the vast majority of cases a mass is palpable and is usually interpreted either as a gallbladder infection or as a liver abscess, especially because in most of these cases there is outspoken subicterus or icterus. The right lung may be partially collapsed so that râles are heard over the posterior region of the lower chest on deep inspiration. These disappear on coughing. There is diminished resonance on percussion. As a rule there is interference with the action of the right dome of the diaphragm so that fluoroscopically one detects a considerably elevated right dome of the diaphragm with respiratory mobility considerably restricted. There is never paradoxical expiratory movement.

There is an accumulation of serous fluid—sympathetic effusion—in the right pleura only when the infection has existed for some length of time. Under such a condition, the abscess may become so encapsulated and hard as to simulate either a carcinoma of the gallbladder, of the right kidney, or of the hepatic flexure of the colon. Only after careful x-ray examination of colon can differential diagnosis be made.

Taking into consideration the symptoms pointing to infection or suppuration, and the other findings, it is advisable to recommend surgical intervention in these cases in order to prevent more serious complications.

Abscess in the Lesser Sac of the Peritoneum.—Occasionally when the suppurative process settles in the lesser peritoneal sac, it may accumulate between the lower border of the liver, stomach and transverse colon. The pain therefore is most intense over the lower and right side of the abdomen. Very often a palpable mass can be detected, indicating the seat of the abscess. The mass may be so large as to press the transverse colon downward or the stomach more to the left, as demonstrable by roentgen examination. Such an abscess may perforate into the peritoneum and give rise to general peritonitis or it may bore its way into the transverse colon and give rise to a fistula of the colon. There are cases on record where an abscess in this location perforated into the stomach and colon, causing a gastrocolic fistula. In addition to local

tion to that of pleuropneumonia, and the absence of such phenomena as a "stitch in the side" and an aggravation of the pain on deep breathing, we suspected that the lesion was in the left subphrenic space as a result of an ulcer that had slowly perforated without giving rise to acute symptoms at the time of perforation. x-Ray examination showed fluid in the left chest, but it was difficult to convince the surgeon that we were dealing with subphrenic abscess. The condition went on for some time until a mass was actually felt. The surgeon insisted this was probably a suppurative carcinoma. Eventually the patient was operated and a subphrenic abscess with considerable suppuration of the spleen was found. Removal of the spleen was necessary. The patient recovered, left the hospital, and has remained comfortable for many years.

PERFORATION INTO A NEIGHBORING ORGAN

The subacute symptoms that ensue when an ulcer perforates slowly into a neighboring organ are due, usually to the reactive changes that occur in the organ into which the ulcer perforates. If the history of perforation is not definite, an erroneous diagnosis of a disease of the organ affected by the perforation is not unusual.

Perforation into the Liver.—When an ulcer perforates into the liver, reactive inflammation of the liver follows, with the eventual development of a liver abscess. The right lobe of the liver is the more often affected if the ulcer is located on the lesser curvature, posterior wall of the stomach.

If the inflammatory changes do not involve the capsule of the liver, the symptoms are slight until suppuration begins. There may be pain in the right side of the abdomen and an elevation of temperature, with or without chills, for weeks without recognition of the condition. The pain, which is increased by breathing, is often referred to the right or left chest, depending upon whether the lesion is in the right or left lobe of the liver. Sometimes there is also spontaneous pain in the right or left shoulder. There are cases on record of so much pain in the right shoulder that the patient voluntarily

One case of this kind was a young man whose ulcer symptoms were obscured by the intensity of other symptoms for more than a year. There was a persistently tired feeling, sub-febrile temperature rising in the afternoon to 100° and 101° F., and a gradually progressive anemia. When the patient entered the hospital, he had marked hematological signs of secondary anemia. Palpation revealed a mass that was at first thought to be an enlarged spleen. It differed from enlargement of the spleen in that it was not freely movable. This immobility was thought by some who saw the case to be due to perisplenitis. We did not concur in this because primary splenomegalic disease of hematopoietic origin rarely, if ever, gives rise to perisplenitis; moreover, enlargement of the spleen in these cases is usually directed as much upward as downward, with dulness extending high into the lateral region of the chest; that is, to about the fifth or sixth interspace. In our case there was definite tympany in the lower part of the chest in the axillary region. There was obliteration of Traube's space. We diagnosed the mass as being a subphrenic abscess, which it proved to be at operation by Dr. A. V. Moschowitz. But, like the history, the surgical findings failed to disclose the cause of the abscess. The patient made a complete recovery and remained well for many years. Then he returned to the office, complaining of typical peptic ulcer symptoms. Roentgen examination revealed a penetrating duodenal ulcer. Dr. Moschowitz operated again, finding the perforated duodenal ulcer that was probably the cause of the original subphrenic abscess.

Occasionally an abscess in this location gives rise to extensive suppuration of the spleen. A case of this kind is a woman in the fifties who had an ulcer on the lesser curvature of the stomach which had given no symptoms for some time. She was suddenly taken ill with temperature, pain on the left side of the chest, and cough. She was admitted to the hospital with a diagnosis of left-sided lower lobe pneumonia with pleurisy. In view of a past history of ulcer and a moderately elevated temperature, as well as constant pain out of propor-

curvature, posterior wall of the stomach perforates into the pancreas and the resulting abscess is small, the systemic symptoms of suppuration far exceed the vague symptoms referable to the pancreas. If the abscess is large, however, local symptoms are the more marked. In this event, there is marked distress and even severe pain in the upper abdomen, which radiates to the back and left shoulder. Glycosuria and progressive ketosis, indicating disturbances in the internal secretory function of the pancreas, occur only when the abscess is large, especially when there is progressive destruction of the tail of the pancreas so that the islands of Langerhans are disturbed. In the vast majority of cases perforation from the duodenum involves the head of the pancreas and, depending on the size of the mass, symptoms of disturbance in the external secretory function are pronounced. The stools are bulky, exceeding the amount of food eaten, are the color of clay, and have a glistening, buttery appearance. Microscopically, the stools show numerous fat globules and no fatty acid crystals, this latter finding being due to diminution or absence of the pancreatic ferment, steapsin. Many muscle fibers are found on microscopical examination. The presence of fat globules (steatorrhea) and muscle fibers in the stools (creatorrhea) especially in the presence of persistent elevation of temperature is indicative of suppuration of the pancreas.

Should the abscess extend to the papilla vateri and to the common duct, jaundice advances rapidly, there is bile in the urine together with a diminution or absence of urobilin and urobilinogen, indicating complete obstruction. Examination of the stool for pancreatic ferments is essential in all cases. The absence of these ferments is a positive sign that the function of external secretion of the pancreas is interfered with by disease of the pancreas, but one must remember that finding these ferments in the stool does not rule out disease of the pancreas. Bacterial activity in the colon can produce results in the stool very much like the ferments. To establish diagnosis, it is well, when possible, to obtain some of the duodenal contents and examine them for pancreatic ferments. Katsch⁴

immobilized the shoulder until disuse atrophy of the shoulder muscles had resulted.

Physical examination nearly always discloses restricted mobility of the lower chest on the affected side. Dulness and diminished breathing indicate the presence of fluid and tend to mislead one to a diagnosis of a primary lesion in the chest, particularly if clear fluid is obtained. If, however, one takes into consideration that despite the presence of fluid the patient has persistent pain in the lower chest and that there is pain in the corresponding hypochondrium, aggravated by deep pressure in this region, a proper diagnosis can be reached. Another positive sign of liver abscess is local and deep-seated pain in the right upper quadrant of the abdomen by pressure over the lower ribs on the right side.

If the abscess is located deep in the liver and there is no sympathetic fluid in the right side of the chest, the mobility of the diaphragm may be entirely normal, although some of these cases have moderate elevation of the diaphragm on the affected side, and even restricted mobility. If the abscess is on the superior surface of the liver, the right dome is invariably elevated and mobility is always restricted. There is often paradoxical diaphragmatic movement. If sympathetic effusion is marked on the affected side, the outline of the dome of the diaphragm is effaced.

In the majority of cases, the abscess continues to enlarge, making clinical diagnosis more certain. There may be intervals when the symptoms are dormant except for an occasional slightly chilly sensation and a slight afternoon rise in temperature, or a rise upon the least exertion. Mild or moderate secondary anemia may develop. An increase in leukocytes with polymorphonucleosis is the rule, but a normal blood count should not be misleading. The abscess is generally encapsulated but in rare cases reactive inflammation around a small abscess may lead to extensive connective tissue formation with absorption of the abscess and spontaneous, complete recovery.

Perforation into the Pancreas.—If an ulcer on the lesser

and deepened rapidly. Soon a mass could be definitely palpated in the right hypochondrium. We diagnosed this as edema of the head of the pancreas. x-Ray examination showed a deformed duodenum and a concavity of the pylorus, which we interpreted as due to pressure from without, probably pressure of an enlarged head of the pancreas. Surgical procedure was advised. At operation, Dr. H. E. Isaacs found such a large mass that it was difficult to determine whether the condition was an inflammatory process in the pancreas or a carcinoma of the pancreas. The duodenum was plastered to the pancreas so that a cholecystogastrostomy had to be performed. The patient rallied from the operation and went home. He gained weight and the mass disappeared.

After a period of several weeks, however, the temperature rose and the patient began to suffer greatly from pain in the upper abdomen. He vomited frequently, the vomitus clearly indicating pyloric obstruction. Jaundice returned.

The patient was readmitted to Beth Israel Hospital and entered with chills, temperature, and a leukocyte count of 25,000 with 92 per cent polymorphonuclear cells. Physical examination revealed a smooth, pulsating mass in the right side of the abdomen, extending from the right hypochondrium to a point on a level with the umbilicus. Believing this to be an abscess of the pancreas, we again advised operation. The mass proved to be a cystic swelling of the head of the pancreas. The findings, together with the history of terrific vomiting, influenced the surgeon to perform a gastro-enterostomy.

The patient improved temporarily, but with the passage of months grew weaker and weaker, and eventually died of exhaustion. An autopsy was performed and an ulcer of the duodenum that had perforated into the pancreas was found. There was also a cyst of the tail of the pancreas and carcinoma of the head of the pancreas.

The question arises, of course, whether or not the patient had a carcinoma of the head of the pancreas when he first came to us. Taking into consideration the hemorrhage four years prior to his first visit, the second hemorrhage with x-ray

advises the introduction of a 1 to 2 cc. of ether into the duodenum to stimulate the flow of pancreatic secretion. A few minutes are allowed to elapse, then the duodenal contents are aspirated. This procedure has a further advantage in that it causes the occurrence of pain in the left shoulder at the time of injecting the ether in cases where the pancreas is involved.

One of the most interesting cases of pancreatic involvement that we have seen occurred in a man forty years of age who developed a second hemorrhage from a duodenal ulcer. He had had no previous ulcer symptoms except the first hemorrhage, four years before, which was diagnosed as due to duodenal ulcer and treated as such.

After the second hemorrhage had subsided (two weeks later), an x-ray examination revealed a distinct duodenal ulcer. The patient's anemia persisted, however, despite a transfusion, and it became necessary to give a second transfusion three weeks after the first. At the end of the second transfusion the patient experienced a stabbing pain in the upper abdomen. This acute pain lasted two hours and then abated, without narcotics. But in its train there appeared a dull pain in the now rigid, distended abdomen. On the following day the distention shifted to the right side of the abdomen. Some of those who examined the patient thought there was a mass in the right ileocecal region but it became evident that perforation had occurred. Immediate operation, however, was fraught with too much danger to be undertaken.

Within three days the patient began to pass many light-colored, bulky stools which, together with the external appearance of the patient, made us suspect an injury to the pancreas. We prescribed a diet of frequent, very light meals, with pancreatin 0.6 combined with 0.6 calcium carbonate after each feeding. The subjective symptoms subsided considerably, but the secondary anemia persisted with the hemoglobin remaining at 38 to 40 per cent. The patient felt well enough to leave the hospital.

During his first week at home he continued to improve, but with the beginning of the second week jaundice appeared.

temic symptoms. When the periduodenal region is affected, a mass generally develops in the right upper quadrant. When the abscess is perigastric a mass is to be found in the midepigastric region above the umbilicus. The mass is extremely tender to touch and pulsatile. Because of the rather superficial location, one may mistake it for an intramural abscess. A differential point is that an abscess in the abdominal wall is more distinctly palpable with the patient in the sitting posture; if intra-abdominal, the mass disappears to palpation in the sitting posture. Operation is obligatory so that if diagnosis is not established before the operation the welfare of the patient is not unduly jeopardized.

PERFORATION WITH CHRONIC SYMPTOMS

A most important group of cases of perforation of peptic ulcer is that where the perforation heals, with the formation of adhesions to neighboring organs. The symptoms may be separated into three groups:

1. Symptoms due to the adhesions proper;
2. Disturbances in the function of the particular organ to which the adhesions extend, and
3. Disturbances in function of the organ (stomach or duodenum) in which the adhesions originate.

Symptoms Due to Adhesions.—Foremost among the general symptoms caused by adhesions is a constantly distressing sensation of fulness in the upper abdomen, amounting to actual pain after a large meal. This is especially so if the adhesions involve the parietal peritoneum. This distress, which abates only at night and not always then, causes the patient to become listless, irritable, and introspective. He develops a capricious appetite and may complain bitterly of obstinate constipation.

When the adhesions originate in a perforated ulcer on the lesser curvature of the posterior wall of the stomach or of the duodenum, there is pain in the back between the eighth dorsal and second lumbar vertebrae. This pain, which is intensified by motion and by the supine posture, is sometimes thought to

evidence of duodenal ulcer, and the absence of jaundice months during his illness, we believe that originally there was perforation of a duodenal ulcer into the pancreas. Whether a rapidly developing cancer of the pancreas occurred on the basis of such irritation is a matter of speculation, but we believe this was the case.

Occasionally, there is perforation of the ulcer into the pancreas without suppuration but causing reactive inflammation. The pancreatic ferment itself causes autodigestion of part of the pancreas and this leads to the formation of a pseudocyst. A case of this nature is one that we saw through the courtesy of Dr. M. Weitzen. The initial acute symptoms were those of perforated ulcer, with pain radiating to the left shoulder and left lower abdomen. The patient improved for a week and then began to suffer severe pain in the left hypochondrium. Roentgen films made elsewhere showed a defect in the pars cardiaca, extending to the upper part of the pars media which was interpreted as carcinoma. After carefully studying the films, we concluded that the defect was due to pressure from without. Palpation revealed a mass in the left hypochondrium and fluoroscopy showed that not only was the left dome of the diaphragm considerably elevated, but its mobility was restricted. In the absence of symptoms or signs pointing to pancreatic involvement, we diagnosed a left-sided subphrenic abscess secondary to perforation of a peptic ulcer. The patient was admitted to Beth Israel Hospital with this diagnosis. At operation, Dr. H. E. Isaacs found a hemorrhagic cyst involving the tail of the pancreas. We believe that the cause of this cyst was the perforation of a gastric ulcer into the pancreas, taking into consideration the acute onset of the condition in the absence of trauma, and the fact that the patient had an early, prolonged history of gastric ulcer symptoms.

Perigastric and Periduodenal Suppuration.—Occasionally an ulcer instead of perforating into an organ perforates directly anteriorly into perigastric or periduodenal tissue giving rise to an abscess. In these cases the history is acute onset followed by the slow, progressive development of symptoms.

hales. The right lobe of the liver is often palpable and tender, and due to persistent suffering the patient may even lose weight and develop a slight secondary anemia. The urine often contains slight traces of albumin and urobilin and in most cases, even if these are absent, a substance may be found in the urine by the Snapper test¹ which, according to Snapper, although not exactly known in its chemical nature, seems to be related to the bile pigments and which when found indicates a mild degree of biliary stasis. Diagnosis is made still more difficult because the dye administered to visualize the gallbladder region shows either a very poorly visualized gallbladder, so that one assumes that the concentration of the dye in the mucous membrane of the gallbladder is markedly diminished, or the gallbladder is not visible at all, even when the dye is given intravenously. It is in these cases that the diagnosis of gallbladder disease is most often wrongly made and the patient submitted to operation for gallbladder disease. The gallbladder is found to be nonpathologic and that adhesions to it have caused such dysfunction as to simulate gallbladder disease both clinically and roentgenologically.

One must assume that this functional disturbance undoubtedly interferes with the cystic duct sphincter (Lutken's sphincter) and prevents the gallbladder from taking up the dye. Roentgenologically one often finds a distorted first portion of the duodenum, the distortion being particularly marked on the greater curvature, the pylorus and duodenum often being pulled to the right and not freely movable on palpation under the fluoroscope. Such a finding, in conjunction with non-visualized gallbladder, gives no clue as to whether the adhesions are the result of gallbladder disease or of perforated ulcer of the duodenum. The adhesions may be so dense that even on the operating table it is impossible for the surgeon to state with certainty where they originated. It may be stated, however, that if the gallbladder is removed in a case of this kind and proves to be entirely without pathology, then the adhe-

¹Snapper Test: To 5 cc. urine, 1 drop of ammonia is added, then drop by drop 1 per cent iodine solution until a light red color develops, add a few cubic centimeters of Schlesinger's reagent; positive reaction is a carmine red.

be caused by chronic spondylitis or by arthritis of the vertebrae if the patient is in the period of life when mild arthritic changes are to be expected.

If the adhesions involve the viscera in the right hypochondrium, there is pain when the patient lies on the left side, due to traction on the viscera.

Pyrosis, regurgitation of sour fluid, and burning under the sternum are nearly always present to a degree out of proportion to disturbance in gastric secretions. Their occurrence bears no relation to meals, unless it be that they are intensified by highly spiced food. This disturbed gastric secretory function is generally due to associated gastric or duodenal catarrh. Another possible cause is that the stomach is continually filled with gas as a result of fermentation which, in turn, has been caused by chronic irritation of the mucosa.

The x-ray examination demonstrates the truthfulness of the patient's statement that he suffers constantly from gaseous distention for the stomach is seen to be filled with gas, often after it has completely emptied itself of a meal.

Functional Disturbances in the Organ Involved by Adhesions.—(a) *Adhesions from Duodenum to Gallbladder.*—The most frequent adhesions after perforation are between the duodenum and the gallbladder. The symptoms point almost wholly to the gallbladder and the erroneous diagnosis of gallbladder disease is the rule. In addition to the general symptoms of adhesions already described, there are attacks of pseudobiliary colic, differing from true biliary colic in that the patient is able to endure the pain without a narcotic. The application of heat to the right hypochondrium may lessen the pain but there is no remission of it in the right intercostal spaces. The entire axillary region may be sensitive to pressure. Pain in the right shoulder is rarely present and pressure over the right shoulder clavicular joint reveals no tenderness. There is tenderness on palpation over the right hypochondrium, especially so on superficial palpation. Percussion tenderness over the right hypochondrium may be brought about in these cases, when the patient forcibly ex-

ingly, leading one to an erroneous diagnosis of gallbladder or biliary duct disease. Examination of the stomach and duodenum discloses, at most, a deformed duodenum with restricted mobility, so that it is impossible to say whether the adhesions originated in the duodenum, gallbladder, or liver. If the patient is operated, the preoperative diagnosis is of adhesions without knowledge of the exact nature of the original injury causing the adhesions. Sometimes the surgeon cannot determine at operation where the adhesions originated.

(c) *Adhesions to the Common Duct or to the Papilla Vateri.*—Occasionally adhesions spread to the common duct or to the papilla vateri and jaundice develops, the degree depending upon the extent of the occlusion. When the occlusion is so complete as to give rise to transient deep jaundice, urobilinogen and urobilin in the urine are diminished. The stagnation of bile in the duct causes biliary colic, simulating the colic of calculous obstruction of the common duct, though less severe.

(d) *Adhesions to the Cystic Duct.*—When there are adhesions to the cystic duct, the most prominent symptom is pain in the right hypochondrium. There is no jaundice. The gallbladder may be so persistently distended as to give rise to hydrops of the gallbladder, making impossible a differential diagnosis between cystic duct obstruction due to stone and obstruction due to adhesions.

(e) *Adhesions to the Pancreas.*—When there are adhesions from the stomach to the pancreas, transient glycosuria is often encountered, and there may be moderate hyperglycemia, but there is never actual diabetes. In some cases the symptoms are those of hyperinsulinemia. One of our patients was a man of forty years who presented all the symptoms and roentgen signs of a perforated ulcer on the lesser curvature of the stomach, with adhesions to the pancreas. The patient had a ravenous appetite, particularly craving sweets. The slightest sensation of hunger produced an intolerable feeling of weakness. Examinations of the blood during these periods showed hypoglycemia (0.05 mg. sugar in the blood). This hypoglycemia was little influenced by the administration of carbohy-

sions almost certainly originated in a perforated ulcer of the duodenum. If the patient succumbs to the operation, the pathologist is able to demonstrate a small, healed, perforated ulcer even though the surgeon was unable to detect it. Occasionally, the presence of the ulcer which perforated may give rise to symptoms years after the operation.

(b) *Adhesions to the Liver.*—When the superior surface of the liver and the right dome of the diaphragm are involved by adhesions, the outstanding symptom is pain confined usually to the right hypochondrium, though sometimes extending to the lower right chest on deep inspiration as well as to the right shoulder. Cases have been reported of such extreme pain in the right shoulder that it has resulted in permanent interference with shoulder motion until the shoulder muscle atrophied.

When the inferior surface of the liver is affected, the liver cells proper may become damaged, giving rise to chronic hepatitis. There is a yellowish tinge to the skin and the skin may be sallow. There is no distinct jaundice. The blood serum contains an increase of liver enzymes. The icteric index is moderately increased. Occasionally there is increased urobilin and urobilinogen in the urine which may also contain a trace of bile.

Physical examination reveals tenderness over the right hypochondrium and a definitely palpable right lobe of the liver. This right lobe of the liver may be tender and somewhat hard, perhaps due to localized cirrhosis. One finds frequently that breath sounds are diminished over the right base, due to local atelectasis of the lung. Another subcrepitant râles are audible on deep breathing, disappearing after coughing. There is often marked pressure tenderness over the right humero-clavicular joint, even in cases where there is not spontaneous pain in this region. There is no tenderness over the right trapezius muscle, in contradistinction to gallbladder infection or biliary duct disease.

Roentgenological examination reveals that in most cases the gallbladder fails to take up the dye or takes it up only spar-

the first half hour no food is seen to leave the stomach and very little food can be squeezed into the duodenum under the fluoroscope. The pylorus may be so rigid and narrow as to simulate carcinoma of the pylorus; only repeated examination clarifies diagnosis. At one examination the stomach may have been hypotonic and then during the stage of acute obstruction show evidence of hypertonicity, the greater curvature situated well above the crest of the ilium, although previously it was below it. The entire stomach takes up the contrast meal, the fornix and pars media sometimes being wider than the pylorus. The small intestine and colon may be situated very low and the stomach very high and transversely situated. Emptying time may be delayed for twelve hours or more.

When the adhesions originate in the pylorus but do not completely occlude it, the symptoms are those of transient pylorospasm. During symptom-free intervals, an error in diet or mental excitement produces digestive disturbances, such as belching, loss of appetite and regurgitation of sour fluid. In the stage of active symptoms, there are frequent attacks of vomiting of large quantities of food eaten as long as ten, twelve or fourteen hours before. Severe pain in the upper abdomen, simulating cholelithiasis, is not uncommon.

An examination of the stomach contents during the symptom-free period generally reveals an abundance of mucus, but little if any alteration in gastric acidity. There may be a tendency toward subacidity.

The x-ray findings when the adhesions originate in the pylorus vary according to when the patient is examined. If during the active period, there is marked gastric retention simulating pyloric stenosis of second or third degree. The stomach is hypotonic or atonic so that the pars media is in the median line and the greater curvature below the crest of the ilium, the pylorus and duodenum being high in the right hypochondrium, often just below the under surface of the liver. Mobility of the entire stomach may be markedly restricted. The pylorus and duodenum are almost immobile. During the symptom-free interval, or a period when the symptoms are

drates; in fact, after a carbohydrate meal only a minute quantity of sugar appeared in the urine. The patient died suddenly in the midst of one of these attacks. We believe that the adhesions to the pancreas stimulated the islands of Langerhans to an overproduction of insulin analogous to that caused by a benign adenoma of the islands of Langerhans described by Wilder.

(f) *Adhesions from the Stomach to the Urinary Bladder.*—This is an extremely rare condition. The symptoms are primarily those of cystitis: frequency of urination and a burning sensation on urination. Because of interference with the function of the urinary bladder there is often actual cystitis that may be so in the foreground as to mask the gastro-intestinal symptoms. Cases have been reported where perforation on the lesser curvature, posterior wall of the stomach has caused adhesions to the urinary bladder and we have encountered one such case, in a patient with a markedly ptosed stomach. In our case the gastro-intestinal symptoms were extremely vague. There was definite history of perforation. The patient complained of frequency of urination and a burning on urination, but cystoscopic examination was negative. *x*-Ray examination of the stomach, however, showed marked delay in emptying and deformity of the pars media resembling incomplete hour-glass of the stomach. We advised operation and Dr. Isaacs operated. A band of adhesions from the posterior wall of the stomach was attached to the urinary bladder and another band from the stomach to the uterus.

Disturbances in the Organ (Stomach or Duodenum) from Which the Adhesions Originate.—Where adhesions deform the stomach or duodenum, the symptoms are chiefly referable to these organs. In most cases, there is associated gastric and duodenal catarrh. There may be intermittent hour-glass formation of the stomach and the more extensive the adhesions the more permanent the hour-glass formation. When pain due to pylorospasm is present, the *x*-ray findings may be those of acute pyloric obstruction, the stomach showing marked hyperperistalsis; sometimes retroperistalsis. During

often cause a deformity of the first portion of the duodenum, leading to progressive duodenal stenosis. The ulcer that leads to chronic symptoms is generally on the posterior wall of the duodenum. The typical symptoms of duodenal ulcer recede and the nausea and frequent vomiting typical of gastric retention make their appearance. There is a constant flow of sour saliva from the mouth and the contents of the fasting stomach show marked hypersecretion. Microscopical examination of the contents shows a residue of food eaten the night before but there is no macroscopical residue. After a test meal, well chymified gastric contents are often obtained, showing excessive secretions and marked hyperacidity. The finding of pancreatic ferments in the stomach contents is an absolute sign that the stenosis is infrapapillary. Of course, pancreatic ferments are present only in vomitus with an alkaline or neutral reaction. Distress and pain in the upper abdomen and right hypochondrium occur whenever the stomach is full and are relieved only by regurgitation of sour fluid, vomiting or gastric lavage.

Diagnosis of the cause of duodenal stenosis is chiefly aided by the x-ray examination. The first portion, and often the upper part of the second portion of the duodenum, may be immensely dilated, depending on the extent of the adhesions; occasionally the whole second portion is dilated. The entire duodenum is dilated if the adhesions extend to the duodeno-jejunal junction. There is deformity, also, of the first portion of the duodenum, depending on the extent of the adhesions. The duodenum is persistently filled in part or in entirety as the food passes through, evidencing active effort on the part of the stomach to empty itself. There is considerable gastric residue after four hours, but after six or eight hours this residue is not as marked as in benign pyloric stenosis. Peristaltic contractions in the duodenum are often seen fluoroscopically. There may be active duodenal retroperistalsis, but there is no gastric retroperistalsis.

Adhesions extending from the first portion of the duodenum to the colon are characterized especially by gas in the hepatic

mild, the stomach is seen to be transversely situated, the pylorus and duodenum being to the right of the median line.

Very often the pylorus is narrower than normal. The duodenum is also narrow and irregular in outline, due in part to adhesions and in part to spasticity. During the symptom-free interval, the emptying time need not be greatly interfered with, the alteration in emptying time being dependent upon atony of the stomach rather than on existing adhesions. If the atony is not marked, the stomach empties on time; but if it is pronounced a residue as late as eight hours after a meal may be detected. That such residue is not due to direct obstruction in the pylorus or duodenum is shown by the fact that emptying of the stomach during the early part of digestion is normal. The stomach tires readily so that in the further course of its activity emptying is retarded. Peristaltic activity is capricious; there may be a short period of hyperperistalsis and then a period of almost complete absence of peristalsis, followed by a period of normal peristalsis. When the patient stands, most of the food is seen in the lower portion of the stomach, very little in the *pars media*.

Occasionally one sees a case of cascade stomach caused by adhesions from a perforated ulcer high on the lesser curvature, posterior wall of the stomach. Cardiac palpitation after meals and extrasystoles when lying on the left side may be so troublesome as to lead the patient to think he suffers from heart disease. Although a suspicion of adhesions may be awakened by persistent pain in the left hypochondrium, aggravated by a little food, and by the fact that belching and hiccoughing are frequently present, the condition can be diagnosed only by roentgen examination. The roentgen findings are positive when the cascade stomach is persistent in a normal or hypotonic individual; when it is not caused by gas in the splenic flexure, or by pressure of an enlarged organ (spleen or left kidney or tumor) on the greater curvature of the stomach; and when there is a large, persistent air bag elevating the left dome of the diaphragm.

Adhesions originating from a perforated duodenal ulcer

with a diagnosis of malignancy of the pylorus, gallbladder or hepatic flexure. There is loss of appetite, obstinate constipation, inanition, anemia and progressive emaciation. In many cases symptoms of avitaminosis are present.

SUMMARY

Symptoms due to perforation of a peptic ulcer have been classified according to the time of onset of the symptoms and their duration. Every perforation is acute, but if it is very small so that it does not spread beyond the peritoneum the acute symptoms may be so mild as to escape attention until subacute or chronic symptoms give evidence that a perforation has occurred. Perforation giving rise to acute symptoms is easily recognized in the majority of cases and even though not diagnosed with exactitude, the surgical nature of the condition is apparent and the patient's welfare is not jeopardized by failure to diagnose the condition before operation. In cases with subacute symptoms, intra-abdominal suppuration may so confuse the picture as to lead to an erroneous diagnosis of the cause of the suppuration. The symptoms that are chronic in nature are often so bizarre that only the most careful history, clinical and x-ray study will lead to the proper diagnosis. Chronic symptoms are influenced by three factors: In what organ the ulcer existed, whether gastric or duodenal; into what organ the ulcer has perforated; and the extent of the adhesions forming as a result of the perforation.

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flexure. Care must be exercised not to mistake the haustra in the hepatic flexure for bands. The symptoms are much more intestinal than gastric in nature. Constipation is extreme. Pain in the right hypochondrium is aggravated when the patient is constipated and relieved only by an enema or laxative. There is marked borborygmi over the hepatic flexure and sometimes over the ascending colon.

Adhesions Extending from the Duodenum to the Duodenojejunal Junction.—Adhesions of this kind give rise to symptoms of acute obstruction of the small intestine. There is severe pain in the upper abdomen. In thin individuals the movements of the coils of the small intestine may be palpated and even seen; in stouter individuals, the gurgling of large air bubbles may be heard over the upper abdomen and over the umbilical region. Vomiting is persistent but does not afford relief. The vomitus consists first of food from the stomach; later bile, and eventually contents of the small intestine having an unpleasant odor and often simulating fecal vomiting. If the symptoms persist and no relief is obtained, collapse manifestations appear. The urinary output is diminished and the urine contains albumin and casts. The alkali reserve in the blood is increased. The chlorides in the blood are diminished. The nonprotein nitrogen is increased. It is essential to recognize the clinical picture because if there is not quick surgical intervention death can ensue within three or four days of the onset of symptoms.

The x-ray examination is of great importance in diagnosis. A finding of coils of the small intestine distended with gas and air is characteristic. Sometimes the distention is so great as to simulate a colon. There is often fluid in addition to the gas, the fluid forming a horizontal level. When one palpates the small intestine during fluoroscopy, this fluid can be seen to move.

Adhesions from a Perforated Duodenal Ulcer to the Gallbladder.—If the adhesions are very dense a palpable mass simulating malignancy is often found in the right hypochondrium. These patients are frequently submitted to operation

The state of acute adrenal insufficiency is also characterized by weakness, prostration, falling blood pressure, rapid thready pulse, nausea, vomiting, dehydration, shock and sudden exitus. Because of this striking similarity to the other disease conditions mentioned, we undertook certain chemical studies in patients suffering from the acute adrenal insufficiency of Addison's disease in order to see if here, too, the blood and interstitial fluids were depleted of basic salts, and indeed, the sodium content of blood from such patients was found to contain even less sodium than is frequently present in patients suffering from dehydration and shock due to the other conditions previously noted. The decreased water content of the blood in severe adrenal insufficiency had been recognized by earlier observers, while Marine and Baumann had in 1927 shown that the blood of adrenalectomized cats contained less sodium than that of normal animals.

The salutary therapeutic effect of sodium chloride in the treatment of cholera was known to O'Shaughnessy in 1832. It was also recognized by Hilton Fagge in 1874 that the intravenous injection of saline solutions was of value in diabetic coma. Both of these clinicians employed this remedial measure in the belief that the collapse resulted from the loss of salt and water from the body. Surgeons have for years known of the benefit of salt solution in the treatment of high intestinal obstruction, though the logical reason for its use in this condition was clarified by Gamble only about ten years ago. Since the replacement of salt and water proved to be a life-saving measure in many other types of salt depletion, it seemed rational to employ the same treatment in acute adrenal insufficiency where a similar physiologic disorder and a similar clinical syndrome were known to exist. That the results were gratifying may be seen from the following case record.

The patient, M. W., a married white woman of forty-one years, entered the hospital on July 16, 1932. She complained of weakness, loss of appetite and weight and increasing pigmentation of the skin, nipples and buccal mucous membranes. She had also had upper abdominal pain from time to

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THE SIGNIFICANCE OF SALT IN THE TREATMENT
OF ADDISON'S DISEASE

CONTINUED drain of salt and water from the blood stream and the reservoirs existing in the intercellular spaces of the body leads to dehydration which may ultimately terminate in the state of shock. This syndrome is characterized by the following signs and symptoms: The patient suffers from profound weakness and often restlessness, nausea and vomiting, his pulse is feeble and rapid, his blood pressure is alarmingly low, and death may follow unless appropriate treatment is instituted. Salt loss, dehydration and shock occur in the course of numerous disease processes and are frequently of primary importance in contributing to a fatal outcome. The mechanisms involved in the development of this state are relatively well understood in many instances. For example, in diabetic acidosis large amounts of sodium from the blood plasma and interstitial fluid, as well as potassium from the cells of the body, are called upon for the excretion of ketone acids. Base and water are also lost in severe glycosuria, even when uncomplicated by acidosis. In patients with high intestinal obstruction the picture of shock develops when large quantities of base and water are lost from the body as a result of protracted vomiting or continuous removal of these substances by surgical drainage. Furthermore, in 1831, O'Shaughnessy recognized that the state of dehydration and shock was frequently the cause of death in cholera and he correctly ascribed this to the diarrheal loss of water and salt.

BLOOD ANALYSES OF THE PATIENT M. W.

Date.	Total base.	Na.	K.	Ca.	Cl.	HCO ₃ .	P.	Glucose.	Serum protein.	Non-protein nitrogen.	Remarks.
		m. eq. per liter	m. eq. per liter	m. eq. per liter	m. eq. per liter	m. eq. per liter	m. eq. per liter	Gm. per liter	m. eq. per liter	mg. per 100 cc.	
7 19 32	136.3	121.5	5.3	5.3	88.6	21.8	2.6	0.73	15.1	39.0	Blood on admission—prostrated.
7 26 32	125.8	107.8	7.1	1.8	72.7	21.5	2.4	0.80	16.9	45.0	In extremis.
8 2 32	147.5	133.0	5.1	5.9	93.8	27.5	2.6	1.20	13.5	20.6	Much better after 1 dose of Eschatin and NaCl therapy.
11 14 32	150.5	139.9	4.6	5.5	107.3	24.3	2.2	1.16	14.4	20.0	Doing part of work at home. Eating salt.
1 24 33	149.5	126.8	5.7	5.6	92.3	21.2	2.5	0.91	16.6	35.0	After seven days salt-poor diet, prostrated and vomiting.
1 30 33	150.1	138.0	5.0	5.2	103.5	25.9	2.2		15.1	25.0	After six days salt feedings. Much better.
4 10 33	149.0	138.0	4.8	5.4	101.4	25.0	2.2	0.85	15.4	29.0	Feeling quite well, taking 15 Gm. of salt daily.
11 9 33		138.0	4.8	4.9	101.2	27.2	1.5		14.6	26.0	Feeling quite well, taking 15 Gm. of salt daily.

time. These symptoms had developed insidiously over a period of two or three years, but had been greatly intensified in the months preceding her admission to the hospital. Physical examination showed the brownish pigmentation of the areas described. The pulse was weak and the blood pressure was 90/60. Auscultation of the lungs showed the presence of scattered, crackling râles, mostly over the region of the right chest, but x-rays of the chest and abdomen were entirely negative. A mild secondary anemia was present. Urine and stool examinations were negative. The patient appeared to be restless and she suffered from insomnia and profound weakness. Her appetite was poor and she vomited from time to time.

Blood studies at this time revealed a sodium concentration of 123.5 m. eq. per liter in contrast with the normal value of 138-140 m. eq. per liter. The chloride and bicarbonate ions were correspondingly reduced in amount. In the course of the next week, the patient's condition became progressively worse, the symptoms already enumerated becoming greatly intensified. Slight dyspnea developed. She became almost pulseless, her blood pressure fell to 65/48, she was in extremis, and the sodium concentration of her blood had fallen to the incredibly low value of 107.8 m. eq. per liter.

The patient was given a single dose of 10 cc. of Parke, Davis and Company Eschatin intravenously, and the administration of salt was begun. She was given about 9.5 Gm. of NaCl a day by proctoclysis and 5 Gm. daily by mouth in capsule form. She was also given broth containing liberal amounts of salt. Within four days the clinical improvement was so striking that the rectal administration of salt was stopped, but the patient continued to take between 5 and 7 Gm. of salt a day by mouth in addition to that included in her diet. In six days, vomiting had stopped, she sat in a chair and was definitely stronger than upon admission to the hospital. Her blood sodium had risen to 133 m. eq. per liter. She continued to gain strength and was discharged fifteen days later on this régime. The patient was seen three months later in the clinic. At this time she was doing part of her housework and had gained 11 pounds. She had vomited but once and complained only of easy fatigability. Her blood sodium was now entirely normal, 139.9 m. eq. per liter. About nine weeks later her condition was unchanged, but because of very slight puffiness under her eyes and slight edema of her ankles at night, she was told to discontinue the use of NaCl and was given a salt-poor diet. This alteration of régime afforded an opportunity to determine whether salt withdrawal would induce acute adrenal insufficiency as conversely salt administration had apparently relieved it. One week later the patient was brought to the hospital requesting readmission. After two days of the salt-poor régime she had become so weak that she was forced to go to bed. For the five days preceding admission she became progressively weaker and vomited at frequent intervals. She had lost seven pounds in one week, her blood pressure had fallen to 86/60 (it was 122/80 the week before) and her blood sodium had dropped to 126.8 m. eq. per liter. She was then given 7 Gm. of NaCl by mouth daily and for three days she received rectal taps of 200 cc. of physiologic salt solution every four hours. *No adrenal cortical extract was administered.* Improvement was striking and the patient was discharged eight days later feeling very well. At the time of writing, eighteen months

establish first that base is excreted and not merely transferred from blood to the tissues, we studied the effect of adrenalectomy upon the electrolyte balances in dogs. From these experiments it became apparent that an extraordinary increase in sodium excretion by the kidneys follows the removal of both adrenal glands and that this increase is amply sufficient to account for the decrease in the sodium content of the blood serum. Harrop has confirmed this finding by noting an increase in the urinary excretion of sodium as adrenal insufficiency develops in adrenalectomized dogs when cortin administration is terminated.

At least three possibilities present themselves to explain this increased urinary excretion of sodium in adrenal insufficiency. First, the loss of sodium might be dependent upon the marked and consistent loss of water from the body. Second, sodium might be called upon to participate in the excretion of large amounts of acid as in diabetic ketosis. Finally, the loss of sodium might be primary, *i. e.*, the adrenal glands might exert a regulatory effect upon sodium metabolism analogous to that of the parathyroid glands upon calcium and phosphorus metabolism. The first of these possibilities seems untenable because it was possible to show that the rate of sodium excretion is augmented out of all proportion to the rate of water excretion following adrenalectomy. Studies on a patient with Addison's disease demonstrated that the urinary excretion of ammonia and titratable acid remained within normal limits while the sodium content of the blood declined and the patient developed the clinical picture of adrenal insufficiency. This observation makes it unlikely that sodium is lost because of increased acid formation. Thus we are left, for the time being, with the hypothesis that the adrenal cortex exerts a regulatory effect upon sodium metabolism through the medium of the kidneys and that when the adrenal glands are removed, the rate of sodium excretion is abnormally increased to the detriment of the whole organism.

It should be emphasized that we do not assume that the regulation of salt balance is the sole function of the adrenal

after her first admission, she has maintained her improvement and complains only of the fact that she usually feels cold and that she tires rather easily. It might be added that she has on her own initiative increased her dose of salt to 15 Gm. a day since discharge from the hospital. Her pigmentation has decreased slightly and her blood pressure is normal, as is the sodium content of her blood serum. The accompanying table gives a summary of the blood studies made on this patient.

We have reproduced these observations on three other patients suffering from Addison's disease with exactly the same results. In every case salt withdrawal induced acute adrenal insufficiency and the administration of NaCl in large amounts greatly relieved the signs and symptoms. There does not appear to be any close correlation between blood pressure level and the sense of well-being, but the latter parallels to an amazing degree the concentration of sodium in the blood. One of our patients died after a period of five months of observation. This patient had active pulmonary tuberculosis and at autopsy the pathologists were unable to find any adrenal cells histologically, the glands being completely replaced by tuberculous tissue. Harrop has confirmed these clinical observations on the therapeutic value of sodium chloride and upon the induction of acute adrenal insufficiency by the withdrawal of salt from the diet of patients suffering from Addison's disease.

From the standpoint of practical therapeutics, it has been our experience that patients with Addison's disease require from 10 to 15 Gm. of salt daily in addition to that of their diet. The amount varies with the severity of the disease and the most valuable therapeutic guide, next to the determination of the sodium content of the blood serum, is the sense of well-being of the patient and the level of his blood pressure. Some patients prefer to take salt in milk and others prefer it in capsule form with meals and with intermediate feedings.

It has been pointed out that several fairly well understood mechanisms resulting in salt loss and dehydration lead to a clinical syndrome similar in many ways to that present in acute adrenal insufficiency. Hence we were naturally interested in an attempt to explain the apparent loss of sodium from blood and interstitial fluid in Addison's disease. In order to



cortex. Salt feeding will not maintain life for more than three weeks in completely adrenalectomized animals. Nevertheless, it cannot be denied that numerous physiologic and clinical disturbances which appear in the presence of acute adrenal insufficiency may be corrected by the ingestion of large amounts of sodium chloride without the addition of any other therapeutic measures. For example, the potassium content of the blood which is elevated to varying degrees in acute insufficiency of the adrenal glands returns to normal levels with salt administration. Nitrogen retention disappears and bicarbonate and chloride concentrations as well as the water content of the blood tend to rise to normal. Salt-treated patients retain most of their pigmentation, they are sensitive to cold and tire more easily than normal individuals and the systolic blood pressure while definitely above shock levels, tends to be low as does the concentration of sugar in the blood. To what part these disturbances may be ascribed to medullary or to cortical insufficiency is not definitely known.

importance is the observation that under standardized and fixed conditions, the rate of uric acid excretion tends to be constant, is uninfluenced by the volume of urine, and is independent of the concentration of uric acid in the blood (Table 1). A constant rate of excretion of any urinary constituent may mean one of two things: Either the kidneys are excreting continuously at their maximum capacity, or the particular product is formed at a constant rate as the result of a metabolic process. As an illustration, when benzoic acid is fed, irrespective of the amount, the excretion of hippuric acid per hour is constant, because the maximum rate at which the body

TABLE 1

RELATION OF URINE VOLUME TO EXCRETION OF CREATININE, SODIUM CHLORIDE AND URIC ACID

Time.	Urine volume.*	Creatinine.	Sodium chloride.	Uric acid.	Urine volume.	Uric acid.†
	cc.	mg.	mg.	mg.	cc.	mg.
10.00-11.00 A. M.	33	59	430	26.7	17	21.3
11.00-12.00	152	60	580	25.0	25	22.8
12.00- 1.00 P. M.	235	59	780	26.0	33	23.6
1.00- 2.00	63	55	490	..	32	22.8

* Diuresis induced by drinking 500 cc. of water.

† 1.0 Gm. of uric acid ingested at 10.00 A. M.

‡ Blood uric acid at 10.00 A. M. 2.4 mg. per 100 cc. of blood.

Blood uric acid at 12.00 A. M. 3.1 mg. per 100 cc. of blood.

synthesizes the glycine to unite with benzoic acid is fixed. If hippuric acid itself is fed, or exogenous glycine supplied with the benzoic acid, the excretion of hippuric acid is increased about 40 per cent, but the rate again becomes constant. It is this latter rate presumably which measures the maximum capacity of the kidney to excrete hippuric acid. The relatively constant rate of uric acid excretion observed during short periods of fast and rest cannot represent the kidneys' maximum capacity, since the excretion can be markedly increased by agents, such as pyruvic acid, which have no known specific action on the kidney. The rate of uric acid excretion seems therefore dependent upon a metabolic process.

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A NEW CONCEPT OF THE SIGNIFICANCE OF URIC ACID IN CLINICAL MEDICINE

IN spite of the vicissitudes of interest in the field of medicine, uric acid until recently retained its position of importance. Now, however, clinical interest in this compound is definitely waning. No doubt this increasing indifference is in part due to the realization that many of the older concepts concerning purine metabolism are inaccurate and probably wrong, and that no comprehensive reinterpretation of the existing information on uric acid has been offered. It is not surprising therefore to find that laboratory data on uric acid is apt more often to confuse rather than help in the elucidation of clinical problems.

In attempting to evaluate the clinical significance of uric acid, it is essential to focus attention on the excretion of uric acid and on the factors that directly influence this mechanism. It seems fairly certain that in the past too much clinical importance was attached to the metabolism of purine-containing foods, and to the breakdown of nuclear material such as leukocytes and other cellular tissues. Likewise it seems that the question whether the human can burn uric acid has received undue emphasis. It is almost certain that man can destroy uric acid but to such a limited degree that when the excretory mechanism is disturbed, uric acid promptly begins to accumulate in the blood.

Before attempting to discuss uric acid findings in clinical conditions, it is necessary to consider the factors that influence the elimination of uric acid in a normal individual. Of prime

of pyruvic acid and other antiketogenic substances, these compounds seem to inactivate the mechanism through which the antiketogenic derivative acts on uric acid. A detailed study of this theory will be presented in a paper which is now being prepared.

Whether this hypothesis is correct is at present essentially of academic interest, but clinically, one cannot ignore the facts that the excretion of uric acid is definitely increased by a certain class of foodstuffs, which can be designated as antiketogenic; and that retention occurs in ketosis, whether the cause be a high fat diet, starvation, diabetes, or merely feeding aceto-acetic acid; in conditions causing disturbed lactic acid metabolism or excess production; and finally in the presence of various aromatic acids such as benzoic acid and phenylacetic acid. In the following discussion, an attempt will be made to show how important these factors are in interpreting uric acid findings in various clinical conditions.

Normal Variations.—Since the excretion of uric acid is related to fundamental metabolic processes, it is easy to understand why marked fluctuations in the concentration of uric acid in the blood can occur in normal healthy subjects. A low blood uric acid is often found after a high protein, high purine diet, which is probably due to the fact that such a diet furnishes an excess amount of antiketogenic material, which stimulates the excretion of uric acid sufficiently to prevent accumulation. On the other hand, any unbalanced diet, one especially high in fat and commonly known as ketogenic, is apt to bring about a sufficient retention of uric acid to increase the concentration in the blood above the accepted normal level, as Harding and his coworkers have demonstrated.⁶ The retention of uric acid after exercise is fairly transient and will probably not lead to confusion clinically.

Diabetes.—It is strange that uric has received relatively little attention in diabetes. Yet it appears very probable that when ketosis appears, uric acid in the blood tends to become elevated. Ricci¹² noted that in fasting diabetic subjects blood uric acid was high in those cases not treated with insulin and

Unlike creatinine, which is promptly excreted when fed, uric acid on ingestion does not increase the hourly output. This indicates that the excretion of uric acid depends on certain factors, which as will be seen later are metabolic. In marked contrast creatinine when once formed is promptly excreted without the intervention of other agents, and the constancy of its rate of elimination is due undoubtedly to the fact that it is produced at a fixed rate.

The important factors which influence the excretion of uric acid can be listed as follows:

Agents Which Increase Uric Acid Excretion.—Glucose in very large amounts can increase the output somewhat,¹ glycerol is more effective,^{1, 2} and pyruvic acid exerts a marked stimulatory effect.^{2, 3} Glycine, alanine, aspartic acid, and glutamic acid also strongly increase the rate of excretion.^{2, 4} A similar effect is obtained by a high protein diet.⁵ All these it will be observed belong to the antiketogenic group of food-stuffs.

Agents Which Decrease Uric Acid Excretion.—1. A high fat diet,⁶ fasting,^{7, 8} and aceto-acetic acid given orally² retard the output of uric acid. These factors have in common the capacity to produce ketosis.

2. Lactic acid when given orally,^{2, 3} produced by strenuous exercise,⁹ by chloroform poisoning, or by excess sodium bicarbonate.

3. Benzoic acid,^{2, 10, 11} phenylacetic acid,² and numerous other aromatic acids decrease uric acid excretion.

In accordance with the foregoing facts, the author has proposed the theory that the excretion of uric acid requires an adequate supply of antiketogenic material. If the quantity of antiketogenic supply is increased, the excretion of uric acid is promptly accelerated, while any diminution brings about a distinct retardation of the uric acid output. Ketosis represents such a depletion of antiketogenic store, likewise excess lactic acid seems to reduce the available antiketogenic material. Since benzoic acid and phenylacetic acid not only decrease uric acid excretion but actually inhibit the stimulatory action

emia can occur in influenzal pneumonia, which often shows a leukopenia, is against this assumption. It seems reasonably certain that the retention of uric acid observed in pneumonia and sometimes in cardiac failure is very definitely associated with the accumulation of lactic acid, and it is probable that this association may also be found in many other conditions such as pernicious anemia, and advanced carcinomatosis. The importance of recognizing this relationship is obvious. Thus, a cardiac condition in which a high blood uric acid is found cannot be diagnosed as cardiorenal unless excess lactic acid is ruled out, or other evidence of kidney damage is present.

It seems fairly certain that the accumulation of lactic acid arises either from overproduction, or from an impairment of the mechanism which reconverts lactic acid to glucose or glycogen. Since the liver is the important organ for this synthesis, it is easy to understand that any injury resulting in hepatic insufficiency can bring about a disturbance in lactic acid metabolism. In eclampsia and chloroform poisoning liver injury undoubtedly is an important factor.

Experimental Alkalosis.—To one schooled in the old way of thinking about uric acid excretion, it seems paradoxical that sodium bicarbonate ingestion should decrease uric acid excretion as demonstrated in Table 2, for excess alkali in-

TABLE 2

EFFECT OF INGESTION OF SODIUM BICARBONATE ON URIC ACID EXCRETION

Time.	Urine volume.	Uric acid.	15 Gm. of sodium bicarbonate ingested at 10.00 A. M.
	cc.	mg.	
9.00-10.00 A. M.	19	27.7	
10.00-11.00	62	25.9	
11.00-12.00	90	19.6	
12.00- 1.00 P. M.	57	19.2	
1.00- 2.00	46	19.0	

creases the solubility of uric acid, and moreover causes a diuresis. It seems pertinent to inquire how sodium bicarbonate can bring about a retention of uric acid. Due to the work of

normal in treated cases; and furthermore, that the elevation of blood uric acid following a high purine diet was more prolonged in diabetic than in normal subjects. Bertram¹³ in a study on diabetes precoma and coma cases found that the blood uric acid was often not only greatly elevated, but frequently so in the absence of increased nonprotein nitrogen. Other studies with similar findings could be cited. One is justified to state that retention of uric acid in diabetes is due primarily to the ketosis, and that it is not a measure of tissue destruction nor is it necessarily an indication of kidney injury.

Eclampsia, Chloroform Poisoning, Pneumonia, Heart Failure, and Conditions of Anoxemia.—At first sight it seems hardly probable that the uricidemia frequently found in this group of diseases could have a common etiologic factor. It should be recalled, however, that lactic acid either when fed or produced by strenuous exercise will definitely diminish the excretion of uric acid. Therefore, if lactic acid in such simple physiologic experiments can cause a temporary retention of uric acid, it is quite probable that a clinical condition in which an excess of lactic acid is formed or accumulates may also show an elevated blood uric acid. In eclampsia, in which a uricidemia was observed by Williams¹⁴ and many subsequent workers, it is well known that an accumulation of lactic acid may occur. It has been found by Stander,¹⁵ Zweifel and Scheller,¹⁶ and others. In a case of chloroform poisoning, Stander¹⁷ found a blood uric acid of 12 mg., and a nonprotein nitrogen of only 65 mg. per 100 cc. of blood. It is common knowledge that lactic acid tends to rise in the blood in this type of liver injury. An accumulation and even excretion of lactic acid is known to occur in lobar pneumonia and has been reported by Holten.¹⁸ It is fairly well accepted that the excess of lactic acid both in pneumonia and heart failure is the result of anoxemia (Jervell¹⁹). Foster²⁰ as well as others noted a high blood uric acid with a normal nonprotein nitrogen frequently in lobar pneumonia. There has been a temptation to explain this finding on the basis of a massive destruction of nuclear material. Of course the finding of Wells²¹ that uricid-

sodium benzoate shows however great variations. Significantly, in certain cases of known hepatic pathology the effect of benzoic acid on uric acid excretion is very striking as illustrated by the following case.

Case I.—(From the Medical Service of Dr. C. F. Tenney.) Miss S., aged twenty-four. At time of admission to the hospital patient was fairly deeply jaundiced. She had no symptoms except a mild anorexia, and no physical findings except jaundice and slight tenderness in the upper right quadrant. Her liver function by the author's test was only 30 per cent of normal, an exceedingly low value. The uric acid output for the four hours following 6 Gm. of sodium benzoate was: 6 mg., 4 mg., 5 mg., and 3.5 mg. One month later she was entirely well clinically, and her liver function had returned to 85 per cent, but the uric acid output after sodium benzoate was 8 mg., 4 mg., 3.5 mg., and 4 mg. In a normal individual the output is much higher as illustrated by a case, picked at random from my unpublished records, in which the excretion was 15 mg., 8 mg., 13 mg., and 18 mg. In the former patient whose condition was diagnosed as catarrhal jaundice, benzoic acid evidently caused an extraordinary inhibition of uric acid excretion. Even after a month when the synthesis of hippuric acid was almost normal, the depression of uric acid by sodium benzoate was still very marked.

The clinical significance of these findings remains to be established, but the potential importance is evident. Benzoic acid, phenylacetic acid and other aromatic acids are constantly formed in the intestines and are even present in certain fruit. In a normal individual their detoxication is so prompt that no retention of uric acid results, but it is entirely possible that a patient with a certain type of liver damage may be unable to conjugate these acids properly and thus suffer retention of uric acid as was illustrated in the above case. One may therefore suggest that any retention of uric acid in the absence of ketosis or excess lactic acid should be investigated from the point of view of a possible chemical toxin and an accompanying decreased liver function. Therapeutically, glycine will accelerate the conjugation of benzoic acid and thereby counteract the uric acid retention. Gelatin, because of its high glycine content, will act similarly on benzoic acid, and in addition since it is antiketogenic will speed the elimination of phenylacetic acid and probably other aromatic acids.

Gout.—Since the author has had no opportunity to study

Macleod and Knapp²² and of Anrep and Cannan²³ one knows that alkalosis results in a marked increase in the production of lactic acid, which in order to be resynthesized to glucose requires, according to the writer's hypothesis, antiketogenic material. It follows that a large excess of lactic acid will exhaust the supply, and it is therefore to be expected that this depletion will not only bring about retention of uric acid, but will ultimately cause the appearance of ketone bodies in the blood and urine, a fact substantiated by the work of Davis, Haldane and Kennaway.²⁴ It is this depletion of antiketogenic material by lactic acid which may well explain the ketosis observed in various clinical conditions of alkalosis such as cyclic vomiting of children. It is quite likely, however, that beside the accumulation of lactic acid the depression of glucose metabolism in alkalosis as emphasized by Haldane²⁵ must also be considered.

It is necessary to digress in order to emphasize the danger of treating ketosis with alkali. Since alkalosis stimulates lactic acid formation, and since there is much suggestive evidence that this compound depletes the antiketogenic store, alkali administration may, if given in sufficient amounts to produce alkalosis, actually intensify the ketosis. Beumer²⁶ claims and probably rightly so that ketosis is aggravated by alkali. It is advisable in any case of ketosis to depend on insulin (with glucose in the nondiabetic cases of ketosis) and on restoration of fluids if anhydremia is present. The acidosis, if not excessive, is very likely to be of more benefit than harm, since there is evidence that the catabolism of glucose to form antiketogenic material is greater in an acid than in an alkaline condition. Adlersberg²⁷ claimed that by feeding acid ammonium phosphate he was able to decrease the urinary acetone and even sugar.

Toxins: Benzoic Acid and Phenylacetic Acid.—On administering sodium benzoate or sodium phenylacetate, the excretion of uric acid drops abruptly and remains below normal until the drug has become conjugated, or in other words, detoxified. The response of various individuals to

urea and creatinine were greatly elevated. One need only mention the series of cases of nephritis reported by Holbrook and Haskins³² in which only 30 per cent showed elevated uric acid, while 86 per cent showed a urea and 60 per cent a creatinine retention. Even Myers and Fine³³ observed cases in which the blood uric acid was normal while the nonprotein nitrogen and urea of the blood was high.

It is evident that uric acid is not the first nitrogen waste product to be retained, for if it were, it should always be elevated when the blood urea is high. It seems reasonably certain that there is no direct relationship between the excretion of urea and creatinine on the one hand, and uric acid on the other hand. Various recent studies indicate fairly definitely that urea and creatinine are excreted via glomerular filtration. At present there is no convincing evidence that in the human uric acid can also be eliminated by means of this mechanism. The fact that the excretion of uric acid is independent of its concentration in the blood, and that the rate of output is readily influenced by agents which exert no effect on the excretion of urea and creatinine, speak emphatically against excretion by glomerular filtration. As stated many times in this paper, the elimination of uric acid is dependent upon a carbohydrate or a derivative of the same. While it is not possible to attempt an explanation of the actual process, it must not be implied that some of the metabolic changes which uric acid may have to undergo in order to be excreted may not take place in the kidney. The fact that this organ can synthesize ammonia, hippuric acid, phenaceturic acid, and probably other conjugated products, that it contains much phosphatase and other enzymes, and that it can readily oxidize ketone bodies (Snapper³¹), is ample evidence for the view that probably a considerable fraction of the excretory work is dependent upon chemical processes which are independent of glomerular filtration.

Suffice it to say that uric acid instead of being the first constituent to be retained may be excreted normally even by a badly damaged kidney. Even in uremia there is a possibility

this disease, he will not attempt to discuss the cause of high blood uric acid which is often observed. It seems safe to surmise that it may be like the uricidemia in eclampsia, merely a manifestation of a pronounced disturbance of a basic metabolic mechanism. At present there is a tendency to consider that gout is an allergic disease and also that a possible liver damage may be an important factor. In view of this, it seems desirable to investigate whether toxins, such as were discussed in the preceding paragraph, could perhaps account for the elevation of the uric acid in the blood.

Nephritis.—It was known by the early investigators that uric acid accumulated in the blood of patients with severe kidney impairment. Garrod²⁸ clearly differentiated between the uric acid retention in gout and in kidney diseases. These older observations were later confirmed especially by Folin with his refined analytical methods. Since uric acid retention was observed in kidney diseases, it was natural to look upon all elevated blood uric acids as indicative of kidney damage. In 1916 Myers, Fine and Lough²⁹ proposed the idea that in the early stages of interstitial nephritis, uric acid retention may be present while the urea, creatinine, and the phenolsulphonephthalein output are normal, or in other words, that uric acid is the most difficult constituent to be excreted and therefore is retained first, while the retention of urea and creatinine occurs only as the kidney damage progresses. This view quickly gained wide acceptance, and was supported by seemingly confirmatory findings from various laboratories. Nevertheless, even in 1913, Folin and Denis³⁰ had emphasized that there was no relation between the amount of uric acid, and of urea or nonprotein nitrogen in human blood. On studying separately the urine of a diseased and a healthy kidney by means of ureteral catheterization, these same workers³¹ obtained results which indicated that the diseased kidney often showed less deficiency in excreting uric acid than the other common nitrogen compounds.

Clinically, it has frequently been observed that the concentration of uric acid in the blood was normal when both

tion of excess lactic acid, which is the normal response to alkalosis. The limitations and dangers of alkali therapy are discussed.

Although uric acid retention occurs in severe kidney conditions, there is no direct relation between its excretion and that of urea and creatinine. The idea that uric acid is excreted with more difficulty than the other nitrogenous waste products and is therefore the first to be retained in interstitial nephritis is not supported by experimental or clinical evidence. Since the excretion of uric acid is influenced by various extrarenal agents, uricidemia does not by itself indicate renal impairment.

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that the retention may not be due to actual structural pathology of the kidney but rather to a toxin, since Becher³⁵ in his studies on uremia has emphasized the great increase in aromatic acids, which, it will be recalled, may cause retention of uric acid. In view of the fact that many extrarenal agents may influence the retention and excretion of uric acid, it seems evident that uricidemia should never be attributed to renal damage unless all other known causes are ruled out.

It is beyond the scope of this paper to discuss the drugs which influence the excretion of uric acid. Since it has been shown that the retention of uric acid is often the result of a disturbance of a basic metabolic process, one must question the value of restoring the blood uric acid to the normal but disregarding the primary cause. It must be remembered that drugs like the salicylates and cincophen have an analgesic action upon which undoubtedly much of their therapeutic usefulness depends. The statement that salicylates and cincophen make the kidney more permeable to uric acid is misleading and in a strict sense probably erroneous. There is evidence that a drug like salicylic acid undergoes certain metabolic changes in the body and it is reasonable to suppose that these chemical changes influence the excretion of uric acid.

Summary.—Uric acid excretion can be accelerated by various antiketogenic compounds; and can be depressed by ketosis, and by lactic acid, whether fed or produced in excess by the body. The elimination of uric acid is markedly inhibited by benzoic acid, phenylacetic acid, and similar compounds.

Clinically, ketosis probably accounts for the uricidemia observed in fasting, in a high fat diet régime, and in severe diabetes; while excess accumulation of lactic acid may explain the high blood uric acid often present in eclampsia, chloroform poisoning, pneumonia, circulatory failure, and various other conditions of anoxemia. The possible significance of aromatic acids in causing uric acid retention in clinical conditions is briefly considered. The uric acid retention after sodium bicarbonate ingestion is most satisfactorily explained by the forma-

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Past History.—Unfortunately the most significant item in the past history cannot be verified. The story usually related states that she began to menstruate at sixteen, the periods recurring monthly for three or four months, then stopping. They never returned. Moreover at twenty-two she was operated upon for "pus in the abdomen." Once or twice she has implied that menstruation was normal until the "ovaries" were removed when she was twenty-two. There is a well-healed hypogastric scar from some abdominal operation and neither the tubes or ovaries can be palpated on bimanual examination. The hospital at which the operation was performed was unable to furnish other information than that she was formerly a patient in that hospital but the record does not state the diagnosis or treatment.

Her brother states that she has been mentally disturbed for seventeen years.

Physical Examination.—The essential findings recorded in the physical examination made at the Neurologic Institute were: "Reflexes equal on both sides; right homonymous hemianopsia; disks pale, more so on the right; corneal reflex on right decreased; tongue is very large, deviates slightly to the left of the midline.

"Systemic findings: Obese, coarse featured, spadelike hands and feet; male distribution of pubic hair; heart and lungs negative; acromegalic type of facies; cooperation very poor, greatly disturbed and suspicious.

"Laboratory findings: Blood count normal; blood chemistry urea, 25.4; sugar, 0.096 per cent; urine negative; blood and spinal fluid Wassermann negative; globulin, 1+; gold curve, 1111110000; basal metabolism, -5.

"x-Ray examination: Right clinoid is quite long and somewhat sharpened. The floor and posterior portion of the sella cannot be identified. There are multiple small areas of calcification just to the right of the sella, extending medially, not unlike plaques of calcification in a vessel. The changes in the sella may be due to pituitary tumor but the calcification is like that seen in the wall of the internal carotid. It may be due to aneurysm. An x-ray of the right hand and wrist shows the ends of the radius and ulna to be rather bulbous; also the distal ends of the metacarpals; there is no thinning of the terminal ends of the phalanges; the distal half of the metacarpals of the little finger has an area of increased density in its medullary portion, about 1 cm. in length, probably an enchondroma."

Due to the marked emotional disturbances and anxiety to return home, the patient had to be discharged before complete examinations were possible; she agreed to return for x-ray therapy.

Second Admission.—The patient returned to the hospital exactly one year later (September, 1932). She refused to discuss her condition, or the progress of her symptoms and stated that she had returned only for operation, nothing else interesting her. Her brother states that during the interval she has had several x-ray treatments and that her mental condition and vision became progressively worse.

Additional facts on reexamination: Odors not named as well on right side Homonymous hemianopsia to the right; pale nerve head on the right with "speckled" appearance. Blurred outlines of the left nerve head. Right pupil larger than left and right reacts poorly to light stimulation. Right cornea

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PITUITARY SURGERY AND MILD DIABETES MELLITUS (?)¹

THE patient was observed on the services of the writers at Metropolitan Hospital.

In order to simplify presentation it has seemed advisable to deviate from the usual order of presentation and develop the facts as they were determined during her hospitalizations.

Miss A. G., aged forty-two, single, white, Jewess, operator of a factory machine.

Chief Complaint.—Double vision and loss of memory.

Present History.—In July, 1931, she noticed impairment of vision in the right eye. The diminution of vision gradually and progressively increased. Early in September of the same year, she suddenly became unconscious while walking on the street and was taken to a hospital. A week later the same event occurred and fortunately she was taken to the same institution. Because of the readmission some studies were instituted and an x-ray "showed a brain tumor." She refused to undergo further study. Subsequently she appeared at the Neurologic Institute and there additional information was obtained. Since 1929 the patient has had seizures characterized by loss of consciousness but without convulsive movements except for licking of the lips and swallowing. At the beginning of the attack the patient begins to run but will remain in any position in which she is placed, until the seizure is over. The attacks last three to five minutes. For the last two years she has tended to walk into doors on her right.

She also complains of headaches that have been very troublesome for the last ten years. They are frequent, but irregular, dull aching in character, usually frontal, more severe on the right side. The site varies somewhat and she thinks that they come from "deep in the head." They are not associated with visual disturbances in the form of spectra nor nausea.

For the last three years her face has become noticeably larger.

¹We are indebted to the Neurologic Institute, New York City, for the report on the tissue examination as well as some of the early findings.

upon, the diagnosis verified and hospitalization continued because of the mental symptoms until July, 1933.

Readmission.—She was discharged from the hospital at her own request late in July, 1933, after having been under continuous observation since her operation. There had been some improvement in vision as judged by her walking, etc., although eye examinations were refused. There was less instability and tearfulness although they could be induced by comparatively minor events. The headaches remained as described above. At home her life was placid and untroubled as far as could be determined and there were no illnesses.

Early in August, about one month after discharge from the hospital she began to drink enormous quantities of water, 30 glasses of water in twenty-four hours not being regarded as unusual at this time. The appetite was fair, the weight unchanged. Two weeks after the polydipsia was noted, the patient began suffering from itching of the vulva which increased in severity and caused her to seek readmission to the hospital early in September.

The analysis of the first specimen of urine voided after admission showed 5 per cent sugar. The twenty-four-hour specimen was acid, 1.034 in specific gravity, chemically and microscopically uninteresting save for 5 per cent sugar. The blood chemistry, the second morning (fasting), was 275 mg. per 100 cc. Blood count showed 4,100,000 red cells, 7200 white cells, 72 per cent polymorphonuclears, 26 per cent lymphocytes, 2 per cent mononuclears. Hemoglobin 80 per cent (Dare).

x-Ray of sella: The floor of the sella turcica appears to be thin and the posterior clinoids irregular. There are two circular bone defects in the right temporoparietal region with a fissure between them and another fissure passing downward and forward from the lower defect. No conclusions.

The blood and spinal fluid Wassermanns were negative.

The basal metabolism was minus 13. The temperature, pulse and respiration remained within normal limits (temperature 98.6° F., pulse 90, respiration 20).

During the next week the patient was placed upon a diabetic régime. Blood sugar examinations varied considerably, the lowest being 300 mg.; the highest 460 mg. Great difficulty was encountered in controlling the patient; food would be taken from the trays of other patients and when arrangements were made to watch her throughout the time of eating, she became markedly unstable, paranoid in her ideas of persecution toward nurses and physicians. She had always been devoutly religious and now insisted on attending services because of the festivals then being observed; on return from the services she would usually admit to the nurse that she had eaten during the service.

She was then placed upon a schema with 70 Gm. of protein, 120 carbohydrates and 100 of fat together with 5 units of insulin morning and night. In two weeks the sugar fell from 390 to 116 and in one week the sugar disappeared from the urine. At this time it was possible to remove the insulin from her régime and the blood sugar remains 100 and the urine sugar free. The diet remained unchanged.

A sugar tolerance test was performed and following the administration of

less responsive than left. The head hair is sparse on top; there is an asymmetria of face, the right lower two thirds appear to be weak. The patient is very unstable emotionally; she cries when the knees are touched; irritable and when confused has paranoid ideas toward the nurses.

The ophthalmologist reported: No papilledema but the appearance of the nerve head and visual fields suggests a pituitary expanding lesion.

Operation consisted of right transfrontal osteoplastic flap with practically complete intracapsular enucleation of the pituitary adenoma. The report on the fresh tissue: Mixed type, pituitary adenoma. Neuropathologic report: Chromophile adenoma of the pituitary.

The patient stood the operation well but was very noisy and confused for a few days thereafter. Mentally the patient improved but the vision and visual fields had not. There was a residual nerve weakness of the sixth nerve on the left side. After two series of deep x-ray therapy she was discharged to convalesce.

History of Interval.—Upon discharge she was placed immediately upon the chronic female neurologic service at Metropolitan Hospital. Daily pulse, temperature and respiration records show no abnormality. The appetite was fair, bowels regular, somewhat loose. Occasionally she complained of vague abdominal cramps which persisted for a few hours. No subjective or objective manifestations were noted in the respiratory tract and save for occasional palpitation the cardiovascular system was negative. Nocturia 1 to 2 was present but had been noted for many years. Frequent urine analyses were negative. She complained of increasing loss of memory, at times gave her age as thirty, at others forty-two. She remained unstable emotionally, often tearful; she was very suspicious of examinations, often refusing to cooperate entirely. No seizures were observed, but an occasional "fainting" was observed. The headache, which temporarily disappeared after operation, recurred. After a few weeks on the service they became daily, usually present in the morning on awakening, and gradually disappearing during the day. At night she was quite comfortable. The headaches are frontal, vertex, dull, constant, and never throbbing.

Summary of the many physical examinations reveals: The pupils are now equal, central, regular and react to light and accommodation. There is impaired motility of the left eye in lateral gaze. Occasionally a questionable nystagmus on looking to the left. The features are definitely acromegalic: The ears large, nose blunt, malar eminences prominent and there is some separation of the teeth in the lower mandible. (These phenomena were of course all evident prior to hospitalization and naturally have not increased after the surgical intervention.) The tongue still deviates to the left and there is weakness of the lower two thirds of the right side of the face. An area of anesthesia is found in the region of the incision, extending from the root of the nose up to the bregma, then to the sagittal suture, along the coronal suture to ear, across and below the right superciliary arch to the beginning of the incision. The remainder of the examination remains as before operation.

In résumé, the patient began with having seizures and disturbance of vision and memory, followed by attacks of unconsciousness which led to a diagnosis of pituitary adenoma; after another year the patient was operated

upon, the diagnosis verified and hospitalization continued because of the mental symptoms until July, 1933.

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sugar the curve remained high (293 mg.) after five hours when observations were discontinued.

The many and excellent studies of Cushing and his co-workers directed the attention of the medical profession to several intriguing problems presented by the pituitary. These studies are so generally known or easily available that there is no necessity for reviewing the literature on this subject. Moreover emphasis has been placed frequently upon the association of pituitary adenoma and diabetes mellitus so often in special articles, that at first sight it might seem presumptuous to report a single case. Nevertheless the case cited presents certain features of interest and is not entirely in accordance with all the usual conceptions and therefore perhaps merits record.

As the appearance of a mild diabetes (?) is the important feature of the case it may be well to discuss this aspect briefly. There appears to be increasing agreement on the frequency of diabetes mellitus in acromegaly, that is, about 12 per cent of the acromegalics have a fairly well-defined diabetes mellitus. There is also a growing conviction that an equal additional number of acromegalics show glycosuria at intervals when subjected to a more prolonged study.

The existence of a neurogenic mechanism in the utilization of sugar has been appreciated ever since Bernard's chemical sugar puncture, seventy-five years ago. More recently suggestive evidence has been presented that the dorsal vagus nucleus, the source of some parasympathetic fibers to the pancreas and sympathetic fibers to the adrenal, is one station in the glycogenolytic process. It seems highly probable that the hypothalamus may represent the site of origin of such responses. It would seem unnecessary to incriminate the pituitary itself in the glycosurias and impaired sugar tolerance after cranial injury. The fact that glycosurias tend to occur with all the better known types of pituitary tumor, even the chromophobe tumors tends to eliminate the possibility of a hyperfunction of some specific group of cell in the pituitary itself. It is generally appreciated that the diabetes of acromegaly, in fact the

form accompanying pituitary basophilism, is insulin resistant. Moreover extract of the posterior lobe, perhaps the vasopressin, diminishes or even counteracts the blood sugar reducing effect of insulin. Finally on the grounds that posterior lobe extract produces a transitory hyperglycemia and glycosuria it has been suggested that the neural portion of the gland is activated in acromegaly; further that compression of this portion by enlarging tumor may account for the spontaneous recovery of a diabetes of acromegaly, or reversely the disappearance of glycosuria after removal of pituitary tumor may be explained by resumption of activity of the compressed gland.

Incidental allusion should be made to certain other common features: If the patient's best story is accepted menses began and ceased at the age of sixteen; if one accepts this age as the date of onset, it would be difficult to understand her shortness or at least normal height. Nevertheless this statement serves to emphasize the importance of amenorrhea as an initial symptom. Although this symptom is usually but not necessarily assigned to the chromophobe tumor, the lesion in this case was a chromophile tumor. To be sure this may be explained by the fact that sex functions are interrupted when the pituitary fossa is greatly expanded by intrasellar pressure, in other words when the basophilic elements have become suppressed by pressure. If this is accepted in the present case it is difficult to determine why a long interval elapsed between the amenorrhea and the appearance of other signs definitely attributable to the pituitary (sixteen years).

The frequent association of acromegaly and increased metabolism should also be mentioned, and the equally frequent association of hypopituitarism with greatly lowered metabolic rate and hypotension. The existence of secondary effects in the adrenal to account for hypertension in some pituitary new growths should be noted in passing.

In view of the paucity of facts, it may seem futile to discuss this case at length although some features deserve brief notation.

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It is the same with the vague abdominal cramps which we attempted to bring into association with her pituitarism. While interest displayed served to increase cooperation, on the least hint of examinations, x-ray studies, etc., the pains would disappear and not recur for many days.

It was impossible to accurately label her psychiatric status. At times it seemed as if her emotional instability might be assigned to the pituitary, or again it might be possible to incriminate the ovariectomy. A diagnosis of constitutional inferiority would not only be incorrect but moreover is hardly informative. However the existence of manifestations in the pituitary, pancreas and ovaries does suggest either a "polyglandular" syndrome of the endocrines or perhaps a constitutional inferiority of the endocrine system. Naturally such a suggestion is highly speculative. However we have seen a family of three sisters who ceased to menstruate in the twenty-eight to thirty-year period, that is, each ceased to menstruate at that age, lost her head hair, teeth, and showed a definite generalized arteriosclerosis. Peculiarly enough all have a bilateral absence of the ulna.

The so-called "seizures" may perhaps be assigned to the pituitary. Perhaps the licking of the lips and swallowing movements can be regarded as equivalents of the gustatory aura of so-called "pituitary epilepsy." The attacks disappeared after surgical intervention, although occasional fainting spells have recurred. We have been inclined to attribute them to psychogenic factors. Certainly none of the picture resembles the diencephalic autonomic epilepsy of Penfield which is characterized by sudden sweating, flushing, salivation, lacrimation, hiccoughing, respiratory disturbances and fall in temperature, in short, by the symptoms of autonomic stimulation.

The sudden onset of marked polydipsia unassociated with polyphagia or weight change was striking. There is a strong but unverified impression that it antedated the polyuria.

Any suggestion in respect to the glycosuria is necessarily speculative in view of the primitive state of our knowledge.

Most cases of acromegaly seek relief before thirty-five and the age in this case, forty, might be considered higher than the usual. However it will be recalled that the diagnosis was apparent on inspection at forty, the facial changes sufficiently pronounced at thirty-nine to attract the attention of herself and her brother who is only slightly more intelligent, so she falls well into the usual age grouping. For statistical purposes it may be well to note that a patient in the same ward presented typical symptoms of acromegaly beginning at fifty-seven. At present (at sixty-two) her weight is 105 pounds over her best weight at fifty-seven. Perhaps she illustrates a type of pathologic overgrowth followed by hypopituitarism, the so-called "fugitive acromegaly" of Bailey and Cushing. In her case the sella is suspicious, the eye grounds negative.

It is highly probable that the diagnosis was possible in her case ten years ago, that is, with the onset of her headaches. At least at the present time a pseudomigrainous headache, occurring for the first time at thirty-two, in a woman with a history of amenorrhea, a headache described as deep in the head, without apparent relation to other factors, unilateral, would certainly excite suspicion and lead to investigation of the visual fields and sella. While the typical sellar localization was absent in this case, the definite association with mental disturbance and psychic confusion is more than suggestive. The mental element, so prominent in this case, made exact description of the headache impossible. Still in cooperative periods and without any suggestion, she would tell how the headache seemed to localize directly in the right eye, a localization frequently encountered in suprasellar involvement. The pain never had the constancy, severity, nor intractable character which we tend to associate with infrasella lesions. Still the headache was quite typical of pressure on the capsule of the gland within the sella rather than a general increase of intracranial pressure. The recurrence of the headache after surgery is likewise of interest. Appreciating that she has undergone a major surgical procedure, our impression is that the psychogenic factor is prominent in her present headache.

When diabetes or glycosuria does occur in the course of acromegaly, it usually appears early. This is contrary to fact in our case.

The contention of some observers is that the glycosuria of acromegaly is thyrogenic in origin owing to the influence of the hypophysis upon the thyroid. It is further contended that the glycosuria is a definite manifestation of an existing hyperthyroidism. It is interesting to note, however, that our patient is one who presents definite characteristic features of hypothyroidism in contradistinction to one with an overacting thyroid gland, and that this is probably due to a glandular retrogression which now reveals itself as a thyroid insufficiency.

It is assumed that in the subthalamie region lies a sympathetic center, which regulates carbohydrate metabolism, and which upon irritation produces a glycosuria. For this reason there are many who believe that hypophyseal tumors produce such pressure irritations which subsequently give rise to the "diabetes" so often found in acromegaly. Yet, frequently one encounters large extrasellary tumors without the slightest evidence of an existing glycosuria or hyperglycemia, in spite of an increased intracranial hypertension and irritation.

Due to an initial overactivity of the hypophysis in acromegaly, there is probably a subsequent hyperactivity of all other organs, and like the retrogression that may occur in the thyroid, a similar retrogression may occur in the other organs alike. Should this process persist, these glands undergo degenerative changes which would similarly affect the pancreatic islands with the inevitable production of a pancreatic diabetes. Whether this is the fact in our patient presented or whether we are dealing with a true though mild diabetes, independent of the pituitary gland, is both the reason for the presentation and discussion of this case.

The age of the patient, the occurrence of the glycosuria years after the initial onset of pituitary symptoms, the fact that she is a Jewess, the existence of evidences of hypothyroidism, the magic-like relief with insulin and diet, particularly when the latter is well controlled, the normal blood sugar and

Owing to the lapse of months between its occurrence and the surgery, it is certainly not the transient postoperative glycosuria, encountered so often in pituitary surgery on experimental animals. The coexistence of a hyperglycemia eliminates the possibility of so-called "simple pituitary glycosuria." Although the statement deserves further examination it is usually postulated that pituitary hyperglycemia is relatively nonresponsive to dietary restriction, whereas this patient reacted with suspicious ease. Instances are recorded in the so-called "pituitary hyperglycemia," in which indulgence of carbohydrates was associated with a lowering of blood sugar. The exact opposite occurred in this case.

The most unfortunate feature of the case, in fact, the item which leads to its report, is our failure to record pharmacological studies on the patient. Attempts were made to study the response to pituitrin intranasally but they merely resulted in removal of the pledgets containing the substance. When other studies were inaugurated to orient ourselves in regard to the parasympathetic nervous system, the patient became confused, noncooperative and resistant, so that they had to be abandoned.

SUMMARY

The case under discussion is that of a woman who presented symptoms of an endocrine dyscrasia of many years' duration. To date there are still in evidence definite acromegaloid characteristics. There suddenly appeared the presence of a glycosuria and hyperglycemia two years after a complete removal of a preexisting benign pituitary adenoma.

It is an almost established fact that acromegaly is associated with involvement of the anterior lobe of the pituitary gland and that acromegaloid symptoms are produced by growths that are not destructive in nature. The growths most frequently responsible for the production of such syndromes are usually benign. It is generally accepted that the anterior lobe is the one involved when an existing glycosuria proves to be pituitary in origin.



urine subsequently, the insulin elimination with the persistence of a stricter dietary régime, proving the fact that the patient is not insulin resistant, all speak for a diagnosis of diabetes independent of pituitary influences, in spite of many features and manifestations of a coexisting acromegaly.¹

¹On November 23, 1933, an attempt was made to secure some photographs of the face, hands and feet of this patient. She suddenly became maniacal, struck the attendants with various objects, so that it was necessary to restrain her. November 24, the patient became more violent and destructive and she was transferred to the psychopathic ward at Bellevue Hospital. Prior to this she had remained sugar free, without insulin and on the usual chronic ward diet, although hyperglycemia could be provoked with ease.

induced by therapeutic procedures based on better diagnosis. Furthermore, the ability to recognize those cases which are at present refractory to therapy makes it possible to prognosticate accurately their probable course, complications and eventual outcome.

APLASTIC ANEMIA

The cases in this group are characterized by persistently low blood levels and a tendency to a progressive, slow, downhill course without remissions or exacerbations. No known therapeutic procedure is efficient in inducing even temporary remissions in this type of case but the course may be prolonged if, by transfusion, the blood levels are maintained at a height compatible with life. Under the general heading of aplastic anemia at least three subgroups may be identified by symptomatic and pathologic differences. Since each of these groups differs in clinical course and prognosis a proper classification of them is important. No attempt will be made to discuss those cases of aplastic anemia which are secondary to known toxic materials such as arsenic, or benzol. Such cases have been frequently encountered and have been described *in extenso* elsewhere.

Case I. Subgroup No. 1, Aplastic Bone Marrow.—A married American housewife of forty-one, entered the hospital complaining of weakness and of bleeding from the gums. The past history was irrelevant except for a supravaginal hysterectomy and bilateral oophorectomy nine years previously. Eighteen months before admission there was a severe attack of a febrile, prostrating disease diagnosed as influenza. Following this her health never returned to normal. She gradually became weak and pale and six months before admission a persistent, mild oozing of blood from the gums appeared. Several transfusions of blood were administered at various intervals without serving to stop the progressive decrease in blood levels more than temporarily. On admission the erythrocyte count was 1,400,000, the hemoglobin (Sahli) 32 per cent, the color index 1.28 and the mean corpuscular volume (Wintrobe), 98 cubic microns. The leukocyte count was 2800 with a differential count which showed no essential deviation from normal. The platelet count was 40,000 and the bleeding time and coagulation time were within normal limits. There was no abnormality of the resistance of the cells to hypotonic salt solution. The serum bilirubin content was within the usual limits. Physical examination showed a middle aged woman in an excellent state of nutrition with marked pallor of the skin and mucous membranes and some evidence of

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THE MODERN THERAPY OF REFRACTORY ANEMIA

RECENT advances in the knowledge of the etiology and treatment of anemia have served as an aid to classification by separating the types which respond easily to therapy from others which are much more refractory. The details of diagnosis and of treatment of such well-recognized conditions as pernicious anemia and idiopathic achlorhydric microcytic anemia are matters of such common knowledge that they no longer afford opportunity for pragmatic experimentation or discussion. Investigation is now directed toward the solution of those hematological problems which fail to conform to the recognized symptomatic or therapeutic classifications. In certain instances the solution is found in more careful and accurate diagnosis based upon a knowledge of the pleomorphic manifestations of the same fundamental mechanisms serving to disturb or to inhibit hematopoiesis. In other cases a diagnosis may be well established and the etiologic mechanism clearly understood but the usual dosage of accepted therapeutic substances administered by the customary routes may fail to effect improvement. In still a third group of cases none of the methods of stimulating hematopoiesis which are known at present are effective in bringing about improvement in blood values. The purpose of this communication is to facilitate an understanding of the fundamental pathologic basis of the various conditions involving persistently lowered blood levels. Such an understanding is of importance to the clinician because it leads to the recognition of those cases, apparently refractory to treatment, in which remissions may be

Iron in a variety of forms was given orally and parenterally without effect. The various components of the blood cells were given orally as a whole and separately. The oral administration of all the known vitamins was pushed to the limit of tolerance and various parts of the normal intestinal tract were fed without effecting any improvement. There was a suggestion that intensive treatment with reduced iron by mouth in amounts up to 6 Gm. daily, increased the interval between transfusions. This possibility was so indefinite that it merits little attention.

Case II. Subgroup 2, Hyperplastic Bone Marrow (Fig. 238).—A married American grocer of fifty-five entered the hospital complaining of pallor and weakness of one year's duration. The past history was irrelevant. The present illness began about one year before entry when he noticed increasing pallor, loss of strength, dyspnea and precordial pain. A diagnosis of "heart disease" was made which was changed to pernicious anemia when examination revealed an anemia of severe degree. The usual therapeutic measures were instituted without relief and repeated transfusions were required to sustain life. On admission, there was an erythrocyte count of 2,350,000, a hemoglobin of 56 per cent (Sahli) and a total leukocyte count of 1000. The mean corpuscular volume was 94 cubic microns, as determined by the method of Wintrobe, and the color index was 1.02. The serum bilirubin content was within normal limits. The platelet count ranged from 40,000 to 60,000. The differential leukocyte count was strikingly abnormal. There was a marked granulopenia with a reduction of the polymorphonuclear cells to 15 per cent or under. From 5 to 15 per cent of B and C myelocytes and 5 per cent of myeloblasts were identified by supravital staining, according to the method of Sabin. The remainder of the white cells were adult, normal appearing, lymphocytes. The stained smear showed marked variations in size and shape of the erythrocytes with a macrocytosis perfectly consistent with a diagnosis of pernicious anemia. From 0.2 to 1 per cent of reticulocytes were constantly present but early erythrocyte forms were rare. The physical examination showed nothing of importance. The patient was in an excellent state of nutrition. There were hemorrhages in the fundi of both eyes. The spleen and liver were not enlarged nor was there any perceptible lymphadenopathy. *x-Ray* studies showed no abnormality of the bony skeleton or of the gastrointestinal tract. No free hydrochloric acid was present in the gastric contents even after histamine injection.

Biopsy of the sternal bone marrow was performed and showed a very red, hyperplastic marrow. Less than the normal amount of bony structure was present. A differential count of the leukocytes in a preparation stained supravitaly gave 19.9 per cent primitive cells. Only a few myelocytes or megaloblasts were seen. Study of fixed and stained preparations confirmed this finding. The marrow was very active with an almost complete replacement of

slight hemorrhage around the gums. There was hemorrhage into the fundus of one eye. x-Ray examination of the bony skeleton and of the gastro-intestinal tract revealed no abnormality. No free hydrochloric acid was present in the gastric contents even after histamine expression.

A biopsy of the sternal bone marrow was performed which revealed a rather bony marrow containing a large amount of fat. Histologically the specimen was found to be composed almost entirely of bone spicules and of fat cells. There were isolated groups of 2 to 3 hematopoietic cells but no suggestion of the active cellular picture normally seen in marrow from the sternum. These pathologic findings were quite in keeping with many reported cases, symptomatically similar to the one under discussion. Such cases have been followed over a period of years during which death from anoxemia has been avoided by blood transfusion until an intercurrent disease finally terminated the course.

. This patient was observed in the hospital for a period of nine months. The use of salvarsan locally on the gums was effective in preventing bleeding. A transfusion of 500 cc. of blood was required about every twelve weeks to maintain an erythrocyte level between one and two millions. There was no essential change in the ratio between the various components of the blood. The stained smears showed moderate variation in size and shape of the erythrocytes with the presence of a considerable number of macrocytes. A reticulocyte percentage of from 0.2 to 1 per cent persisted but nucleated red cell forms were rarely encountered. There were no abnormalities of the leukocytes other than the constant decrease in total number. No evidence of increased hemolysis ever appeared. The patient was discharged unimpaired and her condition has been maintained unchanged for the past six months.

This case is a classical example of the commonest type of aplastic anemia, the group which has a simple aplasia of the functioning bone marrow, rendering it incapable of supplying erythrocytes at a rate great enough to maintain normal blood levels. The marrow aplasia is also shown by the low platelet and leukocyte count. Symptoms, other than those referable to the lack of cellular components of the blood, are few in cases of this type. The tendency to capillary bleeding is slight, although nearly constantly present. The course of this disease is usually prolonged, ranging from months to years. It eventually terminates, without having shown evidence at any time of even a mild, sustained remission. Treatment is of no avail other than the preservation of life by blood transfusion and the control of bleeding from the gums by the local use of salvarsan. This individual received enormous doses of liver extract by the oral, intramuscular and intravenous routes without effect.

with the eventual development of an inhalation pneumonia which terminated fatally. During life there was a slow but steady increase in the number of primitive cells and myeloblasts in the circulating blood and a decrease in the total number of leukocytes. An autopsy was performed and a generalized bone marrow change similar to that seen in the biopsy specimen was found. There was no leukemic tumor, or leukemic infiltration of the organs.

The proper classification of an anemia of this type is difficult. Similar reported cases have been classed with aleukemic leukemia, chronic agranulocytosis and aplastic anemia. Certain striking variations from the typical picture of aleukemic leukemia are present. There is a specific depression of circulating granulocytes with a small number of mature cells of that series. These cells tended to revert more and more toward a primitive cell type. There was at no time an increase or even a normal number of circulating leukocytes. There was no enlargement of the liver, spleen or lymph nodes during life and no histologic infiltration of organs with leukemic tissue at autopsy. The bone marrow showed an inhibition of maturation at the stage of what was considered to be a primitive, pluripotential cell instead of the preponderance of myelocytes seen in ordinary leukemia. For these reasons this type of case differs sharply, in degree at least, from the ordinary aleukemic leukemia. Chronic agranulocytosis is a term based upon one symptom only and should not be employed once the pathologic alterations are known. Aplastic anemia is a poor term since marrow hyperplasia rather than aplasia is present. For clinical purposes, however, aplastic anemia with bone marrow hyperplasia is a useful term. The course in this type of case is always short, the tendency to hemorrhage is marked and the suppression of cell maturation so extreme that frequent transfusions are required. The course tends to be associated with a moderate degree of fever, particularly during the latter stages. No treatment is of any avail.

Case III. Subgroup 3, Hodgkin's Disease of the Bone Marrow (Fig. 239).—A thirty-year-old American salesman, entered the hospital complaining of weakness and fever of five months' duration. The onset of this illness was marked by profuse sweating, fever, loss of weight and pain and swelling about the right tonsil. Periods of high fever lasting three to four

fat by cellular tissue which was surprisingly uniform in histologic detail. The cells were almost all primitive in type with little tendency to differentiate and to mature.

This individual ran a progressively downhill course in spite of any type of treatment. Arsenic in a variety of forms was administered by mouth and parenterally. Liver extract, ventriculin and iron were given in maximum dos-

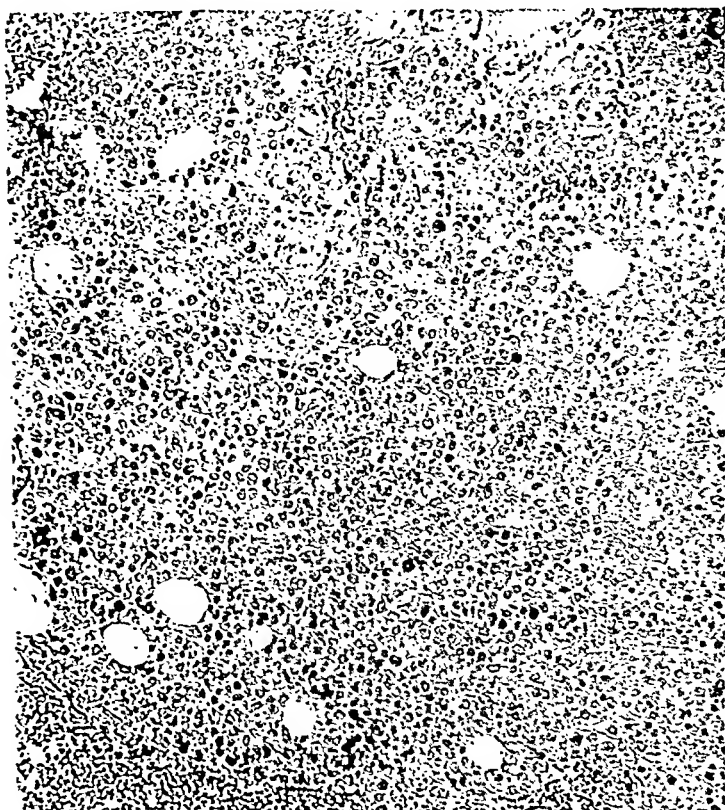


Fig. 238.—Aplastic anemia with bone marrow hyperplasia. Photomicrograph of a section of the sternal bone marrow removed at biopsy from Case II. The normal architecture has been almost obliterated by a very marked hyperplasia of primitive cells.

age and by all possible routes. At no time was there even a temporary remission and transfusions were required at short intervals. Bleeding from the mucous membranes was a difficult problem and could be controlled only by the use of local applications of silver nitrate. Eventually a diffuse cellulitis of the neck developed which yielded *Staphylococcus albus* in pure culture. Intractable hemorrhage from the oral and nasal mucous membranes occurred

seen. There was no deviation of the serum pigment content from normal. The platelet count tended to be low, under 100,000 and the bleeding and clotting time were somewhat prolonged. A biopsy of sternal bone marrow revealed a very firm, white, almost fibrous tissue from which cells for smear preparations could be expressed only with great difficulty. Study of smears stained supravitaly showed a predominance of myeloblasts and myelocytes but examination of the fixed and stained preparation showed a typical histologic picture of Hodgkin's disease with islands of myelopoiesis. One of these islands had clearly been encountered in making the smear preparation. A lymph node removed at the same time from the inguinal region showed the typical changes of Hodgkin's disease although it was only slightly enlarged.

This individual became rapidly worse, the anemia was profound and blood transfusions were required frequently to maintain life. Hemorrhage into the skin and eyegrounds appeared. Death occurred five weeks after entry. At autopsy typical Hodgkin's disease of the bone marrow, spleen, liver and all lymph nodes examined was found.

This case is one of a group which hitherto has been classified as aplastic anemia of unknown etiology, reticulo-endotheliosis (Damashek) or aleukemic leukemia. Since the presenting picture is one of anemia without a tendency to regeneration and since the usual manifestations of Hodgkin's disease such as the enlarged liver, spleen and lymph nodes were not prominent it seems most suitable to include this case as one of aplastic anemia due to Hodgkin's disease of the bone marrow.

The clinical course was marked by its rapidity, the recurrent fever, the loss of weight, the profound anemia with almost no blood cell production on the part of the marrow and the relatively slight tendency to hemorrhage into the skin and mucous membranes.

SECONDARY ANEMIA

Case IV. Depression of Bone Marrow Secondary to a Focus of Infection.—An unmarried American female laboratory technician entered the hospital complaining of pallor and weakness of five years' duration.

The disease began with progressive weakness and pallor. Examination showed a microcytic anemia of marked degree with a hemoglobin level of 55 per cent. In spite of persistent treatment with iron, copper and magnesium the hemoglobin percentage decreased until a level of 30 per cent was reached three years before entry. At that time the spleen was removed after two blood transfusions had been given. Following the operation there was a rise in hemoglobin to 80 per cent but gastro-intestinal disturbance with sore-

days began and persisted throughout the course of the illness. On entrance, the physical examination showed a pale individual with evidence of marked loss of weight. There were a few palpable lymph nodes in the cervical and inguinal regions measuring about 1.5 by 1 cm. The liver and spleen were not enlarged. There was no free hydrochloric acid in the gastric contents even after the administration of histamine. There was no abnormality shown by



Fig. 239.—Aplastic anemia due to Hodgkin's disease of the bone marrow. Photomicrograph from a section of the sternal bone marrow removed at biopsy from Case III. The normal structure has been completely replaced by tissue characteristic of Hodgkin's granuloma.

x-ray examination of the skeleton or of the gastro-intestinal tract. The erythrocyte count was 2,450,000, the hemoglobin 39 per cent, and the leukocyte count 2350. The color index was 0.885 and the mean corpuscular volume 78 cubic microns. A supravital differential count showed that only about 20 per cent of the cells were of the granulocyte series. From 2 to 4 per cent of B and C myelocytes were present although no younger forms were

liver extract. A mild remission followed and therapy was discontinued. An exacerbation occurred not long afterward and no benefit followed the oral administration of liver extract in heavy dosage. Relief was obtained, however, by the intramuscular injection of similar material. Once more treatment was discontinued and symptoms recurred. Intramuscular treatment with an amount of a liver extract preparation which was derived from 100 Gm. of liver was administered on alternate days for five weeks without improvement. The patient entered the hospital in extremis, with an erythrocyte count of 840,000 and a hemoglobin of 22 per cent. There was a color index of 1.37

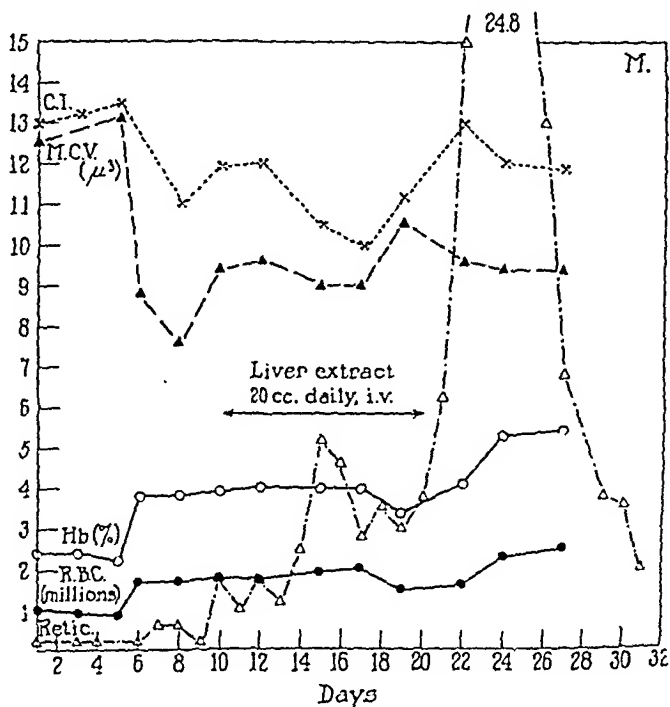


Fig. 240.—Pernicious anemia refractory to ordinary therapy. Chart showing the increase in blood levels following intensive intravenous therapy.

and a mean corpuscular volume of 120 cubic microns. The total leukocyte count was 2050. The reticulocytes numbered 0.6 per cent and there was no deviation of the differential white cell count from normal. There was marked variation of size and shape of the erythrocytes in the stained smear but no immature forms were present.

The physical examination showed an almost comatose individual with evidence of marked loss of weight. The skin and mucous membranes were pale and the sclerae showed a rather yellowish tinge. There was no tendency to bleed into the skin or mucous membranes and there was no enlargement of the liver and spleen. Because of the failure to respond to what would

ness and focal inflammatory lesions of the tongue and mouth began to be present. Examination of the blood at this time showed a change of the type of anemia from microcytic to one marked by macrocytosis. Persistent intravenous and intramuscular injection of liver extract supplemented by iron by mouth failed to improve the blood levels, although the oral symptoms subsided. Six months before entrance persistent dull aching pain in the face appeared and drainage of the accessory nasal sinuses was performed without relief. On entrance to this hospital the physical examination showed a pale, thin girl in obvious discomfort. The spleen had been removed and there was no enlargement of the liver or lymph nodes. Examination of the blood showed the erythrocytes to number 2,500,000, the leukocytes 12,500, and the hemoglobin to be 71 per cent (Sahli). The mean corpuscular volume was 126 cubic microns and the color index 1.30. The unstained smear showed a distinct macrocytosis and the differential leukocyte count was within normal limits. Since the materials effective in relieving this type of anemia had been administered up to the limit of tolerance it was considered that some factor inhibiting the effect of these substances must be present. Careful examination disclosed an infected ethmoid cell from which a pure culture of hemolytic streptococci was obtained.

Biopsy of the sternal bone marrow disclosed tissue of about normal cellularity and bony structure. Histologic examination showed an active marrow with the cells in the various stages of development present in the normal ratios. This picture of increased activity with a normal distribution of the various cell types had been encountered previously in cases where maturation and delivery to the circulation had been inhibited by infectious or toxic processes. A radical drainage of the infected ethmoid cell was performed and following this procedure there was a steady rise in the blood levels and improvement in the sense of well being. Eight weeks after admission the patient was discharged with an erythrocyte count of 4,520,000 and a hemoglobin level of 81 per cent.

This case is an excellent example of the inhibition of hematopoietic activity resulting from a relatively small focus of infection in an accessory sinus. No antianemic treatment was administered until an improvement in blood values following eradication of the infective focus had been established. Then liver extract was injected intravenously each week until normal blood levels had been obtained.

REFRACTORY ANEMIAS OF KNOWN CLASSIFICATION

Case V. Pernicious Anemia (Fig. 240).—A sixty-year-old American machinist entered the hospital complaining of weakness and dyspnea of two years' duration. Two years previously he had noticed increasing pallor, dyspnea and loss of strength. His physician established a diagnosis of pernicious anemia and instituted adequate therapy with orally administered

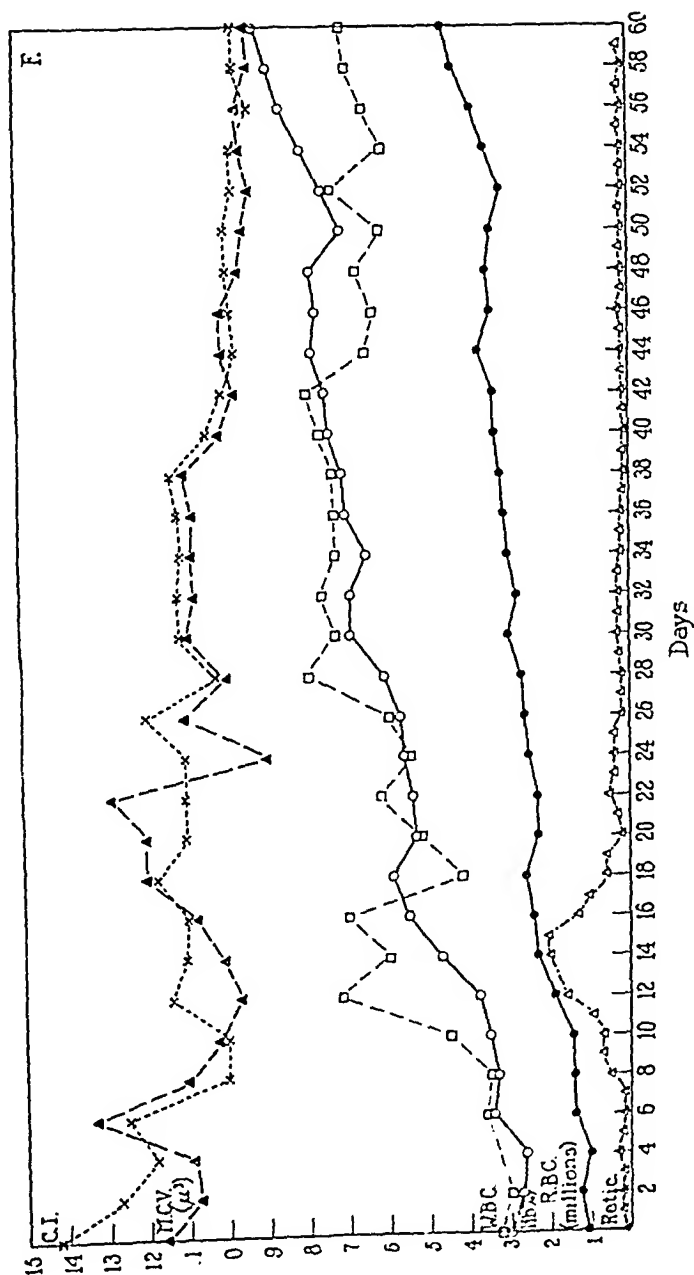


Fig. 241.—Sprue anemia refractory to ordinary therapy. Chart showing the increase in blood levels following intensive parenteral therapy.

membranes. A diagnosis of tropical sprue was made. She came to this country fifteen months before admission but in spite of this move the diarrhea continued and weakness and pallor appeared. She entered another

ordinarily be an ample dosage of liver extract administered parenterally the diagnosis was in doubt and a biopsy of the sternal bone marrow was performed. The tissue was deep red and hemorrhagic with a diminution in number of the bony trabeculae. Supravitaly stained smears showed many megaloblasts and primitive cells with a moderate number of granulocytes in normal phases of development. The preponderance of megaloblasts was so striking that a diagnosis of pernicious anemia was unavoidable in spite of the failure to respond to apparently adequate therapy. It was decided to institute extremely intensive treatment by the parenteral route on the assumption that a quantity of effective substance sufficient to raise the concentration in the blood to more than threshold levels had not been administered. Accordingly 20 cc. of liver extract, an amount derived from 100 Gm. of whole liver, was injected daily by the intravenous route. On the tenth day following the institution of this therapy there was a sharp rise in the percentage of reticulocytes which reached a peak on the twenty-fourth day and then rapidly fell to normal. This was followed by a rapid rise of erythrocyte and hemoglobin levels and a fall in the color index and mean corpuscular volume. The patient was discharged well six weeks after admission.

This case is a striking example of the development of a state of pernicious anemia in which ordinary therapeutic methods are completely useless. This individual received without effect many times the amount of liver extract which would be sufficient to effect a maximum response in the ordinary case. Without the histologic examination of the bone marrow which disclosed changes pathognomonic of pernicious anemia the case would probably have been classified as an aplastic anemia and treatment would have been discontinued. At present there is no adequate explanation of this phenomenon. Study of experimental deficiency disease shows a distinct tendency for animals on a continuous mild dietary lack to require progressively larger dosage of the required dietary constituents to effect relief of symptoms. Such an explanation may be at the basis of pernicious anemia which is refractory to the ordinary therapeutic dosage of liver extract.

REFRACTORY ANEMIAS OF KNOWN CLASSIFICATION

Case VI. Sprue.—A married Puerto Rican-born housewife of forty-seven entered the hospital complaining of weakness and diarrhea of four years' duration. The onset of the symptoms occurred while she was a resident of Puerto Rico. Bouts of diarrhea of gradually increasing frequency and intensity occurred with a gradual progressive loss of weight, abdominal discomfort, and some soreness and redness of the lingual and buccal mucous

divided into three subgroups according to the pathologic processes which have affected hematopoiesis. In one, an aplasia of the blood-forming cells has taken place. The clinical picture of this group is marked by a relatively slight disturbance of the general health except for symptoms due directly to the anemia, little variation in the ratios between the various types of leukocytes in the circulating blood, and a general depression of the cellular blood components. There is a mild tendency to capillary bleeding. The clinical course shows no tendency to spontaneous remissions.

The second subgroup of aplastic anemia is associated with a hyperplasia of the cellular elements of the bone marrow with an inhibition of maturation at the stage of a primitive cell type which is presumably pluripotential. This pluripotentiality is assumed both from the morphology of the cell itself and from the fact that both the red and white cells of the circulating blood are markedly decreased in numbers. This group of cases shows a striking tendency to necrosing lesions of the mucous membranes of the mouth and rectum and to indolent, infiltrating infections of the subcutaneous tissues with organisms ordinarily benign. Fever of a low-grade, intermittent type is present. The tendency to bleeding into the eyes and from the mucous membranes is pronounced. The peripheral blood shows a color index and average erythrocyte volume somewhat greater than normal without an increased serum bilirubin. There is a marked depression of the total leukocyte count and particularly of the granulocytes. Some myelocytes are frequently present but more frequently very young cells of the myeloblast group are found. The white cell count never rises to normal levels and the clinical course is progressively downward. No leukemic tumor or leukemic infiltration of organs is found at autopsy. Hence, a simple diagnosis of aleukemic leukemia is not justified by the clinical course or by the pathologic findings.

The third subgroup of the aplastic anemias is one associated with an infiltration and replacement of functioning bone marrow by tissue characteristic of Hodgkin's granuloma. The

hospital where she was stated to have a severe anemia of the type of pernicious anemia. Various sorts of dietary therapy were tried without effect. The patient's condition steadily became worse and parenterally administered liver extract was advised. Accordingly, an amount of liver extract derived from 10 Gm. of whole liver was administered intramuscularly each day without relief of symptoms. The patient appeared moribund and she was admitted to this hospital. Physical examination showed an emaciated woman, incontinent and irrational, having almost continuous diarrhea. The abdomen was distended and thin-walled. There was no enlargement of the liver and spleen nor was there evidence of skin or mucous membrane hemorrhage. The erythrocytes numbered 900,000, the hemoglobin (Sahli) 24 per cent, the color index 1.33 and the mean corpuscular volume 122 cubic microns. There was no abnormal variation of the serum bilirubin content. The leukocytes numbered 2700 with a normal differential count. The stained smear showed considerable variation in shape and size with a predominance of macrocytes. The cellular morphology was quite consistent with that of pernicious anemia. In view of the desperate situation an amount of liver extract derived from 100 Gm. of whole liver was injected daily by the intramuscular route. Until the tenth day the patient's condition grew steadily worse. On that day, however, there was a striking symptomatic improvement coincident with a rise in the percentage of reticulocytes which reached 25 per cent on the fourteenth day. The diarrhea ceased, the patient regained consciousness and by the third week after the institution of therapy a full blown remission was in progress. From that time on progress was steady. There was a gain of 40 pounds in weight, complete absence of gastro-intestinal disturbance and a restoration of normal blood levels. The patient was discharged from the hospital well and with regular injections of liver extract has remained in good health for eighteen months.

This case illustrated once more the necessity for heavy dosage administered by the proper route in a case which had failed to respond to ordinary therapeutic methods. The typical clinical picture of sprue with a macrocytic anemia made possible the determination to persist in known specific treatment until results had been obtained. Without a clear comprehension of the nature of sprue and of the specificity of liver extract administered in adequate dosage by the proper route, treatment would have been abandoned and a fatal outcome would have resulted.

DISCUSSION

Clinical examples of three principal types of anemia have been presented which were refractory to ordinary therapeutic methods. The first group, that of the aplastic anemias, may be

quirement for the specific substances used in treatment has appeared. The development of this state is assumed to be analogous to a similar situation encountered in animals on diets lacking in particular essential substances. If the deficiency has been prolonged and if only enough treatment has been administered to control acute symptoms a need for progressively greater dosage becomes manifest. The clinical examples of this sort of a refractory condition cited include one of pernicious anemia and one of sprue. In both instances the diagnosis was obvious but the failure to effect a response with ordinary therapy tended to shake the confidence of the physician in the accuracy of the diagnosis. Only persistent intensive therapy by a parenteral route sufficed to effect a cure.

In brief, the successful treatment of cases of refractory anemia depends upon accurate diagnosis, upon an understanding of the pathologic changes present, and upon pushing an indicated therapeutic procedure to a point at which results are obtained. As long as these principles are adhered to the maximum number of successful therapeutic results will be obtained.

presenting symptoms in this group is anemia of a severe degree associated with leukopenia and the presence of a certain number of immature leukocytes in the blood stream. Here again the color index and the mean corpuscular volume are somewhat elevated and the serum pigment content is not increased. The clinical course is rapidly downward and marked by sharp elevations of temperature and by loss of weight. Lymphadenopathy either transient or permanent and of a mild degree may be present. There is very slight tendency to hemorrhage. At autopsy evidence of generalized Hodgkin's disease is found. Since the presenting symptom of this condition is disturbed hematopoiesis it is classified with the aplastic anemias. In none of the three subgroups of aplastic anemia are any therapeutic procedures known at present which are effective in inducing even the most mild remission. The progress varies widely with the pathologic process but in all three is bad as regards the ultimate outcome.

The second main group of refractory anemia cases includes those in which the effect of ordinary antianemic measures is inhibited by the presence of a toxic or an infectious condition. Examples of this situation are frequently encountered. The bone marrow shows a normal or an increased cellular content with the different varieties of cells present in normal ratios. The color index and mean corpuscular volume is usually somewhat greater than normal so that the picture may simulate a mild degree of pernicious anemia or of macrocytic anemia. Ordinary measures directed toward the improvement of blood values are ineffective until the condition inhibiting hematopoiesis is removed. In the clinical example cited no method of treatment was effective until an infectious focus in an ethmoid cell was removed. Not infrequently a similar basic mechanism is encountered in cases of nephritis, where no improvement in blood levels can be brought about until the urea clearance is increased.

The third main group of anemias which are refractory to ordinary treatment is one composed of cases in which the diagnosis is clear but in which a state of abnormally high re-

upper air passages known as coryza or the common cold. Although relatively little is known as to the real etiology of this common condition, research appears to be making some progress in this direction. It is however not generally recognized that a common cold is not simply an inflammation of the nasal mucous membrane, but that even in its mildest form some of the accessory nasal sinuses, especially the ethmoids, are almost uniformly involved, with a latent infection frequently remaining after the acute symptoms have disappeared.

In addition to this common cause of latent infection in the upper air passages we have other latent infections especially in the tonsils, in the nasopharynx and at the roots of the teeth. These conditions predispose to the recurrence of acute infections either from a lighting-up of their latent condition or because of an increased susceptibility to new infections from the outside.

Another predisposing factor is the obstruction to normal nasal breathing, caused by such conditions as adenoids or large tonsils, deviations of the nasal septum, and nasal polyps. These conditions predispose to infection not only because they harbor latent infections themselves, but because they interfere with the normal filtration function of the air passages.

It thus comes about that almost every one has some abnormal condition of the upper air passages, and is therefore in varying degree susceptible to respiratory infections.

The Most Frequent Upper Respiratory Conditions with Which We are Concerned, in Addition to the Common Cold or Coryza, are Sinusitis, Diseased Tonsils and Adenoids, and Infected Teeth.—These frequently cause no symptoms for months at a time, sometimes result in a more or less continuous condition of nasal catarrh, with frequent acute exacerbations, and are of course much more frequent in the winter season when variations of temperature are greatest and variations in the weather are common and opportunities for exogenous infections are greater because of more continuous indoor-living and closer contact with other people.

Instances of Infection of the Bronchi and Lungs.—

CLINIC OF DR. JAMES ALEXANDER MILLER

BELLEVUE HOSPITAL

THE RELATION OF THE UPPER AIR PASSAGES TO CERTAIN CHEST CONDITIONS

Introduction.—With all of the obvious advantages which have accrued to the practice of medicine through the development of specialism, there is always some danger that through overspecialism the study of disease may be so strictly divided into various compartments that the relationship which exists between various diseases, and particularly between various organs of the body, may be overlooked.

In no sphere of medicine is this more obvious than in the case of the respiratory system. The diagnosis and treatment of diseases of the upper air passages have become very largely a matter of strict specialism, while the diseases of the chest belong to the internist or to the specialist in lung diseases. Too frequently the particular specialist to whom a patient first applies for treatment, is neglectful of symptoms which may be chiefly due to conditions in the other field of specialism.

It is, of course, well known that the respiratory system from the nose down to the alveoli of the lungs consists of continuous air passages lined by a continuous mucous membrane which is easily affected by extension of infection from one portion of the system to the other. Such a common symptom as cough, for example, may be caused by irritation in any part of this respiratory system, and may be associated with definite lesions in either or both the upper and lower respiratory tract, and successful treatment often depends upon the recognition of this fact, with appropriate remedial action.

Instances of Upper Respiratory Infection.—Probably the most frequent of our minor ills is the infection of the .

severe and frequently lead to permanent impairment of lung function even when death itself does not result from the acute infection. Exactly similar results may be expected in a certain number of cases of less severe infection by the ordinary and usually less virulent organisms causing respiratory disease, particularly the streptococcus, pneumococcus and the influenza bacillus, and some of the less usual types of bacteria.

Subacute Bronchopneumonia and Peribronchitis.—

As already indicated, many of these cases with rather slight constitutional disturbances are really suffering from a mild form of bronchopneumonia. This usually clears up promptly, but occasionally runs on into the more chronic forms, and in children may cause permanent impairment of bronchial function, which may lay the foundation for other respiratory diseases of adult life, particularly bronchiectasis.

Closely associated with this type of bronchopneumonia which can be readily recognized by roentgenological examination at the time of the acute disease, there is a type of respiratory infection the exact pathologic nature of which is not well understood and which has been variously described under such terms as peribronchitis, nontuberculous respiratory infection, or as subacute bronchopneumonia. This clinical entity is usually accompanied by very mild constitutional disturbance, and most frequently owes its origin to previous or associated infections of the upper air passages. In such cases the lesions are usually in the lower lobes, but are generally unilateral.

The symptoms are those of cough and expectoration, sometimes even slight hemoptysis, and the physical signs are those of numerous moist râles over a considerable portion of one lobe, usually a lower lobe. These signs may persist for many weeks, even long after not only the constitutional symptoms but also the cough and expectoration have disappeared; they are often mistaken for tuberculosis. The differential diagnosis is made from the acuteness of the onset, the extensiveness of the physical signs associated with very slight constitutional disturbances, the absence of tubercle bacilli in the sputum and the presence of various forms of acute respiratory

The chest conditions with which we are concerned because of the possible influence of affections of the upper air passages, are fairly numerous and may be taken up separately.

Acute Bronchitis.—This is the most common chest condition resulting from respiratory infection. Every practitioner is familiar with the type of child or young adult who is susceptible to frequent colds associated with bronchitis, evidenced by cough, expectoration and a greater or less degree of constitutional disturbance, usually of short duration. Such a bronchitis very frequently has its origin in infections of the upper air passages, particularly in cases where there are present some of the abnormalities of the upper respiratory tract which have already been discussed. Unless this relationship is recognized and the original source of the infection removed, treatment of these recurrent attacks of bronchitis is simply palliative, and more or less frequent recurrence of the condition is to be expected.

Acute Bronchopneumonia.—Many of these acute infections are not limited to inflammation of the bronchial tree, but extend down into the parenchyma of the lung, resulting in bronchopneumonia. As in the case of bronchitis, these lesions are usually bilateral and in the lower lobes of the lungs. The constitutional symptoms are more severe than in bronchitis, but the association with the infection in the upper air passages is frequently the same. It is perhaps not sufficiently widely recognized that many of the cases which we are accustomed to think of as simple cases of bronchitis, are really mild cases of bronchopneumonia. This can easily be proved by x-ray examination at the time of the acute febrile disturbances. Frequently such bronchopneumonias are not very severe and are of comparatively short duration, although, of course, many other cases result in very acute illness or even in death itself. This is particularly apt to be the case in children.

The coincidental infection of the upper air passages and the lungs is, of course, very frequently seen in acute infectious diseases, particularly measles, influenza and whooping cough, and in such cases bronchopneumonias are very apt to be more

allergic phenonema known under the general term of hay fever, has long been recognized. The same thing is true of abnormal sensitization to certain food proteins. In other cases and even more frequently, however, the sensitization appears to be to bacterial proteins, and very commonly the focal bacterial infections which produce this sensitization are in the upper air passages. This is particularly true, of course, in connection with the infections of the accessory nasal sinuses, especially those which result in the formation of nasal polyps and obstruction to nasal breathing. In such cases, of course, only either the removal of the foci of infection or the desensitization of the individual to the bacterial protein can lead to permanent relief of the asthmatic condition.

Bronchiectasis.—We have already mentioned bronchiectasis as one of the possible sequelae of some of the more acute and less serious affections of the bronchi. It is perhaps not sufficiently recognized that true bronchiectasis is very apt to have as its underlying cause impairment of the function of the lung and bronchial tree in early childhood, due to one or another of the respiratory infections. Such impairment of function makes subsequent infections of the bronchi more easy and their effects more persistent and damaging. But even when this condition has occurred, there are no symptoms, and no disability is caused unless subsequent infection occurs. Probably in most individuals some such damage of lung function occurs during childhood, but comparatively few develop bronchiectasis. It is in the cases where a chronic persistent infection of the upper air passages leads to recurrent infections of the lower respiratory tract that real damage is done, and the gradual infection of the walls of the bronchi, with their dilatation, results.

A well-developed case of bronchiectasis is one of the most discouraging medical conditions to treat. The hope of the future lies in prevention of the conditions by a wider appreciation of the etiologic relationship between these conditions and those milder forms of respiratory infections which are so often associated with the upper respiratory tract and which

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sleep, but very frequently is seen where a person has been rendered unconscious, as for example during an accident or in an epileptic fit; or through prolonged opportunities for infection without the opportunity of cough, as seen in cases of submersion.

After a pulmonary abscess has been formed, its treatment fortunately now is fairly well standardized, so that no longer is the mortality so very high, but it still constitutes a very serious disease. It would appear that an appreciation of the methods by which these infections occur, leading to greater care during operations on the upper respiratory tract, and particularly to generally improved prophylaxis as to infections of the mouth and throat, would lead to a very definite diminution in the incidence of this condition.

Other Incidental Correlations Between the Upper Air Passages and the Chest. The Effect on Pulmonary Tuberculosis.—Current medical opinion appears to have accepted the notion that acute respiratory infections are very apt to stir up or reactivate quiescent or latent lesions of pulmonary tuberculosis. This has led to a very definite dread on the part of patients with pulmonary tuberculosis lest they should develop colds and the like, also the fear of such acute infections as influenza and its results on tuberculous patients, and finally to the doctrine that pulmonary tuberculosis as activated by acute respiratory infections or irritations occurring during occupation, may lay the basis for compensation for the economic loss of such tuberculosis where the irritations or infections have occurred in industry.

All of these opinions appear to be based upon erroneous assumptions. There is little or no evidence that even acute respiratory infections, such as acute influenza, have any marked effect upon the underlying tuberculous process. Certainly there is none that the irritation produced by the inhalation of gases produces any such aggravation. This has been well demonstrated by the gassing during the war, in which practically no cases of active tuberculosis developed following such gassing.

can be permanently relieved or prevented by appropriate treatment.

Abscess of the Lung.—Pulmonary abscess may be caused either by infection through the respiratory tract or, less frequently, by an infected embolus, through the blood stream, from some other part of the body. By far the most common cause is infection through the respiratory tract.

It was formerly considered that lung abscess occurred as the breaking-down of a case which was originally one of pneumonia. We now know that many of these cases are suppurative processes from the start, without going through the phase of an exudative pneumonic process. Clinical and experimental evidence also teaches us that this infection is most frequently associated with some infection of the upper air passages, and bacteriological studies have emphasized the particular danger which lies in infection of the upper air passages with certain anaerobic organisms which are very often found in the crypts of the tonsils, in the roots of abscessed teeth, or in the crevices of a chronic sinusitis.

The frequency with which lung abscess follows some operation upon the upper respiratory tract has long been recognized. At one time this was thought to be due to the kind of anesthetic used. Later it was considered to be simply an aggravated form of postoperative pneumonia, but it is now known that these abscesses do not usually occur unless infection from the upper air passages gets into the lungs because of blood which is allowed to enter the trachea at the time of the operation. The operations following which pulmonary abscesses are most apt to occur are tonsillectomy and extraction of teeth, and it is just these two conditions in which chronic anaerobic infection in the mouth is usually present, and the resulting lung abscess is due to the infection of the inhaled blood by these organisms. In other cases chronic sinus infection may lead to the same kind of suppuration in the lungs.

In cases in which there has been no operation, the cause of the pulmonary abscess is probably the inhalation of infected mucus from the mouth and throat, which may occur during

irritating to a case of acute rhinitis, pharyngitis and bronchitis than it is to a case of pulmonary tuberculosis, and the irritating effects of such smoking frequently aggravate and prolong these conditions. The same is, of course, true of exposure to more irritating gases or fumes.

The Effect of Fresh Open Air.—The wide dissemination of antituberculosis propaganda has done much to foster the habit of open-air living. It is, of course, now recognized that the effect of fresh air is not due to the breathing of the air but rather to a reflex effect from the surface of the body. The general acceptance of the principle of out-of-door life for the treatment of pulmonary tuberculosis has led to its adoption for many other conditions, and where the individual has a vasomotor tone that responds normally, good results have followed.

It is, however, perhaps not sufficiently recognized that cold fresh air, as particularly associated with drafts or air currents, has a definitely irritating effect upon acute respiratory infections, especially those associated with congestion of the mucous membrane. In such cases, whether it be a cold in the head, an acute sore throat, or bronchitis, or an acute exudative form of influenza, exposure to too low or changing temperatures and air currents, such as one finds out of doors or with wide open windows, is definitely to be avoided.

The Effect of Improper Indoor Conditions.—Just as the out-of-door conditions may have variable effects depending upon the condition of the respiratory mucous membrane, so it is true also in connection with indoor conditions. This problem is largely associated with the problem of proper ventilation of homes, schools, workshops or other places of indoor assembly.

The apparent abnormal amount of acute respiratory infection in this country, particularly of sinusitis, has often been ascribed to the overheating and poor ventilation which are common in American homes. Certainly it is true that any individual with an abnormal condition of the upper respiratory tract leading to greater or less obstruction to normal breathing, will be more susceptible to variations both of weather and of temperature. It is also true that in such cases under the influ-

What is perhaps important to realize is, that coincident with such a slight infection as a cold in the head, a patient with pulmonary tuberculosis will have an increase in the moist sounds which can be heard in the chest over the lesions during the time of such an infection. This may be associated with slight temporary increase of cough and expectoration, and the fact that more and moist râles are heard at the time leads to the assumption, on the part of inexperienced physicians, that there has been an activation of the tuberculous lesion. Careful study of such cases will show that this increased moisture is temporary and rarely, if ever, leads to an exacerbation of the lesion itself. It appears to be simply an expression of the fact that the respiratory mucous membrane is a continuous one, and that increased congestion of the upper respiratory tract is associated with a similar condition in the lungs and bronchi. A very interesting corroboration of this fact is furnished by the observation of Graham and Singer of definite increase in the secretion from bronchial fistula during a period of acute upper respiratory infection, and this without any aggravation of the lung lesion itself.

It is important, therefore, to watch such cases of pulmonary tuberculosis through their attack of acute infection before jumping to the conclusion that there has been a real reactivation of the lesion itself. The best guide is the roentgenological examination which practically invariably fails to reveal any increase of shadows during or after such attacks.

The Effects of Inhalation of Vapors, Gases, Smoke, Etc.—We have already discussed the effect of such inhalations upon pulmonary tuberculosis, and what has been said concerning irritating gases, to a very considerable extent holds good for tobacco smoke inhaled in the ordinary habit of smoking. Within limits of moderation the lesions of cases of pulmonary tuberculosis do not appear to be irritated by the use of tobacco. Quite the contrary is, however, the effect of such inhalation upon the acute respiratory infections, whether these infections be of the upper air passages or of the bronchi and lungs. The inhalation of tobacco smoke, for example, is distinctly more

iliarize themselves with the ordinary manifestations of upper respiratory conditions which so often seriously affect, or may even cause, the diseases of the chest in which they may be primarily interested.

ence of such changes, exacerbation of latent infection of the upper air passages seems to be more common. Here, too, we are probably dealing more with reflex action from the skin rather than with a local effect on the upper respiratory tract itself. This has lately been very interestingly studied by Leonard Hill in connection with his experiments concerning the various kinds of heat upon the sensation of stuffiness in the nose, in which he appears to have demonstrated that this condition is entirely a reflex from the skin and is dependent upon the kind of heat produced and also upon the character of the individual mucous membrane. All of these observations have their importance in centering attention upon the improvement of ventilation conditions of indoor-life, and particularly, of course, during the winter season when opportunities for contact infection are greater and variations of temperature and, consequently, congestion of the mucous membrane of the respiratory tract, with greater liability to infection, occurs.

Conclusions.—The observations which have been offered concerning the relations between the upper respiratory tract and the chest, lead us to consider whether as physicians we have sufficiently recognized the close association between the upper and lower respiratory tract, and whether with all its advantages specialism has not led to certain errors in practice, which are preventable. The correct diagnosis of conditions in the upper air passages or in the chest is often dependent upon an appreciation of what is going on in the other end of the respiratory system.

But more important than this even is the fact that the causation of these conditions is often dependent upon a closely related affection the existence of which may have been unrecognized because it appears to belong within the sphere of another specialty of medical practice. And, lastly, most important of all, that any efforts to treat successfully or to prevent these conditions must depend upon a study of the respiratory tract as a whole, so that nose and throat specialists can never afford to neglect the chest and, on the other hand, that internists and specialists in chest diseases should make every effort to fam-

logical series of deductions disfigured neither by empty hypothesis, nor by untenable and wild speculations." This same reviewer goes on to say, "This is what we want in medical reasoning. Let nothing be argued upon until it is proved; let no fact be received until its truth is established; then and not till then, will medicine rank as a science, and the disputes and cavillings of its professors become susceptible to adjustment according to exact and incontrovertible data."

Turning next to the therapeutic implications which naturally follow from the biochemical disturbances found to be present in the disease, Dr. O'Shaughnessy states that the cure is seemingly dependent upon two principles: "First, to restore the blood to its natural specific gravity (*i. e.*, its water content); second, to restore its deficient saline matters." He then states that, "The first of these can only be affected by absorption, by imbibition, or by the injection of aqueous fluid into the veins. The same remarks, with sufficiently obvious modifications, apply to the second." The practical application of these principles was described as follows: "In severer cases copious enemata of warm water, holding the natural salts of the blood in solution are strongly recommended. . . . When absorption is entirely suspended the author recommends the injection into the veins of tepid water holding a solution of the normal salts of the blood. Thus it is apparent that one hundred and one years ago a physician with an investigative and critical mind was able, with the crude methods at his disposal, to unravel the mechanism of the essential manifestation of cholera, *viz.*, dehydration, salt depletion and shock. Furthermore, he logically employed the specific therapy indicated by such a disturbance in physiology.

Although the implications of O'Shaughnessy's brilliant work were confirmed by a number of workers at home, as well as on the continent, the struggle to overcome the traditional prejudices of those in authority is beautifully exemplified by the following words written by Dr. J. Pidduck to the London Medical Gazette, August 21, 1832.

"Turning hopelessly away from the Central Board and

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DEHYDRATION AND MEDICAL SHOCK

IN 1831, Dr. W. B. O'Shaughnessy of Newcastle-upon-Tyne, wrote a brief letter to the London Medical Gazette which embodied the results of several years of what he termed his "experimental inquiries" into the cholera. His terse summary of a physiologic mechanism in terms of what we choose to call modern chemistry is a delightful contrast to the usual clinical sophistry of that day, and perhaps this, and compels us to quote his communication *in toto*.

"1. The blood drawn in the worst cases of the cholera, is unchanged in its anatomical or globular structure.

"2. It has lost a large proportion of its water, 1000 parts of cholera serum having but the average of 850 parts of water.

"3. It has lost also a great proportion of its *neutral* saline ingredients.

"4. Of the free alkali contained in healthy serum, not a particle is present in some cholera cases, and barely a trace in others.

"5. Urea exists in the cases where suppression of urine has been a marked symptom.

"6. All the salts deficient in the blood, especially the alkali or carbonate of soda, are present in large quantities in the peculiar white dejected matters."

We think you will agree with a contemporary reviewer of Dr. O'Shaughnessy's "Chemical Pathology of Cholera" who in the Lancet of 1832, called particular attention to the "strictly

the like treatment in the collapse of cholera." The importance of this observation was nine years later overshadowed by Stadelmann's discovery of the existence of an acidosis in diabetic coma. Stadelmann quite logically felt that the replacement of alkali was the obvious point of attack. This concept so completely dominated the treatment of diabetic coma that even the more modern textbooks omit mention of the clear correlation between dehydration and circulatory collapse which Fagge had demonstrated in 1874. One must not neglect to state that for at least twenty-five years salt solution has been routinely employed in the treatment of diabetic acidosis. However, it was believed that the picture of low blood pressure, thready pulse, oliguria and collapse resulted from "toxic" cardiac failure rather than from shock due to decreased circulating blood volume and vasomotor paralysis. In recent years it has been shown that the loss of salts and water in diabetes is dependent upon two unrelated mechanisms. One of these is the obvious loss of base resulting from the excretion of ketone acids. The other is definitely associated with the occurrence of severe glycosuria, and may be found even in the absence of ketosis, but the nature of its underlying physiologic disturbance is not known.

The clinical picture dependent upon dehydration, salt loss and consequent shock is found in many other disease conditions. Prominent among these is the group characterized by pyloric or high intestinal obstruction, as well as those patients in whom for some reason there exist fistulous openings to the upper gastro-intestinal tract or the bile ducts. It naturally follows that the picture of shock in these patients results in part at least from constant vomiting or persistent drainage of body fluids normally rich in sodium salts. It should be pointed out that in certain cases of intestinal obstruction no actual loss of salt from the body occurs, but the same result is effected by the outpouring of salts and water into the distended loops of intestine, thus removing it from the circulating blood and tissue spaces. The chemical changes in the blood under these conditions, *viz.*, decreased water, sodium and chloride content and

Local Hospital, I resolved to pursue the experiment (*i. e.*, saline therapy) among the poor in my district, convinced that the brandy and laudanum system had been too highly recommended, and too long sanctioned by authority, to admit of the introduction by the same individuals of another system so diametrically opposed to it. Perhaps such a revolution in a cherished opinion, and a favourite practice, would be a stretch of candour and liberality almost superhuman."

In spite of the fact that in 1850, the German biochemist Karl Schmidt confirmed and greatly amplified the analytical results of O'Shaughnessy there were subsequently but occasional references to the value of intravenous salt solution. It was not until Rogers, and Nichols and Andrews in 1909, used intravenous saline injections with remarkable decrease in mortality in a cholera epidemic in the Philippine Islands that this rational form of therapy became generally accepted.

We have taken time to trace the development of the chemical pathology of cholera because it presents probably the earliest instance in which there was an understanding recognition of the physiologic processes involved in the development of this common complication of many disease conditions, *viz.*, dehydration, salt depletion and shock. Furthermore, it was in the treatment of cholera that, for the first time, a rational replacement therapy was instituted with, we might add, the anticipated clinical benefit.

Chronologically, the next correct appraisal of the fundamental problem may be found in the Guy's Hospital reports of 1874. Dr. C. Hilton Fagge described, therein, "A Case of Diabetic Coma, treated with partial success by the injection of a saline solution into the blood." The most impressive feature of this pioneer experiment in therapy was the rationale which he offered. This is best expressed in his own words, "What suggested to my mind the advisability of injecting a saline solution into the blood in this case was the idea that coma was due to the drain of water from the system, caused by the diabetes. I suppose that the hypothesis upon which I acted was essentially similar to that which formed the basis of

salt from the diet of patients who were in relatively good clinical condition as a result of salt therapy. It is truly remarkable to observe the difference that 15 Gm. of salt a day will effect in the health and well-being of such a patient. It has been demonstrated in our laboratories that the decrease in salt content of the blood in adrenalectomized dogs is due to an enormous increase in the excretion of sodium by the kidney. This loss of sodium is accompanied by an augmented but not parallel water output and results in the characteristic picture of dehydration, salt depletion and shock. It seems likely that the mechanism by which salt depletion and dehydration are produced in adrenal insufficiency is different from the disturbances resulting in shock in the clinical conditions described previously. On the basis of the evidence so far accumulated we are inclined to believe that the active principle of the adrenal cortex exerts a controlling influence upon sodium metabolism through the medium of the kidney, and that the breakdown of this regulatory mechanism results in an increased rate of sodium excretion. That the regulatory effect of the adrenal cortex upon salt and water metabolism is not its sole function is proved by the fact that adrenalectomized animals eventually succumb although the period of survival may be appreciably prolonged by salt administration.

It is apparent from the foregoing discussion that the loss of water and salt from the body may occur in a variety of ways and result from a number of different physiologic disturbances. Among these we have described: loss of base and water by diarrhea, vomiting or surgical drainage; loss of serum by exudation in burns; loss of salt in the urine by alterations in the carbohydrate metabolism; loss of salt as a response to acidosis and finally, an excessive urinary excretion of sodium in adrenal insufficiency. It might be well to add the obvious statement that the simplest form of shock resulting from salt and water depletion is that due to acute hemorrhage. There is one common denominator to be found in all of these disease conditions, when they have reached an advanced state, viz., the shock syndrome.

increase in urea, have been recognized for many years. Furthermore, clinicians have for a long time appreciated the therapeutic value of intravenous salt solution. The original hypothesis assumed that the condition was due to a toxemia and that the saline therapy acted as a detoxicant. It remained for Gamble, about ten years ago, to show that for pyloric obstruction, at least, no other factors than salt loss and dehydration were to be found. In other words, as in cholera and diabetic acidosis, striking clinical improvement follows the replacement of salt and water.

Another situation in which shock plays a dominant rôle is found in the sequelae of severe burns. Of course, we recognize that there are probably several factors which may contribute to a fatal outcome, but certainly the one which today has greatest therapeutic possibilities is that resulting from dehydration and salt depletion. Serum exudation in the burned areas is an important component of the mechanism of this dehydration. The cause of the characteristic acidosis has been ascribed to the presence of certain unknown acids, but it may possibly be due to a loss of sodium and consequently a lowering of the blood bicarbonate. However, the nature of the complicated disturbances resulting from severe burns cannot be well understood without further chemical study.

The clinical syndrome of acute adrenal insufficiency as seen in Addison's disease bears a striking resemblance to that present in the other pathologic states which we have discussed. For example, weakness, prostration, rapid pulse, nausea and vomiting, fall in blood pressure, decrease in water content of the blood, increase in blood urea and decrease in the concentration of chloride and bicarbonate are characteristic. We have shown that in adrenal insufficiency in man, the sodium of the blood is markedly lowered, as Marine and Bauman and also Zwemer had shown in cats. Furthermore, we were able to show that the administration of sodium chloride alleviates to a striking degree the clinical manifestations just described. On the other hand, it is possible to precipitate an acute and alarming attack of adrenal insufficiency by the withdrawal of

at the American Museum of Natural History was bitten on the back of his hand. In spite of the immediate administration of antivenom serum the patient collapsed in twenty minutes and was brought to the Presbyterian Hospital. On admission he presented an extraordinary picture. His skin was cold and dusky red in color, he was semicomatose, his respirations were shallow, his pulse was rapid and almost imperceptible, his heart sounds were inaudible and his blood pressure was too low to be read. In spite of several saline infusions and a transfusion of 700 cc. his blood pressure, which was raised by these therapeutic procedures, soon fell to a critical level again. It was not until 7200 cc. of fluids had been given intravenously in the course of sixteen hours that his blood pressure remained normal. The almost invariably fatal outcome from an intravenous rattlesnake bite results from failure to recognize the fact that the therapeutic attack should be primarily directed against the state of shock.

When Laennec, in 1826, described the weakness of the heart sounds in severe febrile conditions, he attributed this change to cardiac failure, a point of view which, unfortunately, still continues to dominate medical thought. This is true in spite of the fact that Romberg and Pässler as early as 1899 wrote upon the effect of bacterial products on the vasomotor apparatus of rabbits. These authors were able to show that a state of collapse could be induced by the intravenous injection of pneumococci or other organisms. Furthermore, they pointed out that intravenous salt solution was more effective in treating these animals than was subcutaneous ether, camphor, strychnine or cognac. Romberg at that time suggested the term "toxic shock" for this complication of infectious disease. It is hardly necessary to emphasize the similarity between Romberg's "toxic shock" and the shock resulting from intravenous injections of histamine or snake venom.

A striking confirmation of the shock-producing capacity of the pneumococcus was afforded by a clinical experiment performed upon himself by a member of our staff a few years ago. This individual gave himself a large dose of pneumococcus

We should like now to consider briefly the train of events by which dehydration and salt depletion ultimately lead to the classical syndrome of shock. One of the most striking physiologic principles of the body is expressed in its tenacious effort to maintain the salt content of the blood serum and the interstitial fluids at a constant level in the face of amazingly adverse circumstances. Thus, when salt is lost for any reason, the body sacrifices its precious water stores to protect its sodium concentration. Conversely, the extensive loss of water is almost invariably associated with a considerable loss of salt. Now, severe drain of salt and water from the tissue spaces is reflected in the circulating blood, producing in time a decrease in blood volume so great that the state of shock ensues in much the same manner as in acute hemorrhage. Therefore, we are led to infer that the state of shock is the physiologic result of an acute disparity between the circulating blood volume and the functioning capacity of the vascular bed. This may be brought about in one of two ways; either by a relatively rapid decrease in the circulating blood volume or by sudden expansion of the vascular bed. In the clearest example of the former, *viz.*, acute hemorrhage, the decrease in blood volume is obvious, and the ensuing results have been adequately studied. In the other conditions which I have discussed, the mechanism is analogous to hemorrhage but there are many complicating factors still to be elucidated.

Let us now turn our attention to those situations in which the state of shock is brought about primarily by a rapid dilatation of the vascular bed rather than by contraction of the blood volume. Since the isolation of histamine by Sir Henry Dale in 1909, physiologists have recognized that large doses of this drug will cause a generalized capillary dilatation, drop in blood pressure and collapse. Of greater importance to the clinician is a discussion of those states in which this mechanism results from natural disease processes, rather than the artificial laboratory experiment. It was the privilege of one of us some years ago to observe the clinical effect of an intravenous rattlesnake bite. This patient while extracting venom

inevitably accompanied by an increase in the size of the capillary pores which permits large quantities of blood serum to escape into the tissue spaces. Thus, the component of decreased circulating blood volume also plays a part. This effect may naturally be assumed to exist in the case of snake venom and bacterial capillary poisoning, or in any other condition in which generalized capillary dilatation is marked.

In diabetic acidosis accompanied by the shock syndrome, we have indicated the importance of dehydration and salt depletion. We have all seen patients in whom the state of shock has persisted after adequate replacement therapy and after the ketosis had disappeared. There is experimental evidence which suggests that there may be in these cases a factor of capillary poisoning which is responsible for the persistent recurrence of the shock syndrome. It has been shown that certain substances which have a chemical similarity to the ketone bodies, for example, acetyl acetone and sodium acetate, will produce vasodilatation in animals.

There has been much discussion of the participation of a toxin in the production of the clinical manifestations of intestinal obstruction and, indeed, substances with histamine-like action have been isolated from damaged loops of gut. To what extent these substances contribute to the total mechanism in producing shock is still problematical. We have pointed out the rôle of dehydration and salt loss in severe burns but here, too, certain toxic substances are perhaps absorbed from the necrosing tissue and may act as capillary poisons.

It seems possible that there is still another mechanism involved in the production of shock through vasodilatation, though our understanding of the process is still obscure. We refer to the influence of the sympathetic nervous system. This is dramatically demonstrated in the production of traumatic shock. Although severe and extensive traumatization of tissue results in a certain amount of dehydration by serous exudation and hemorrhage, it has been reported that injury to a limb isolated from the rest of the body except for its nerve supply may result in shock. Thus it would appear possible to

vaccine, intravenously. There followed an immediate and alarming collapse during which his systolic blood pressure fell to 60 mm. of Hg and continued below normal for three days. In conjunction with this he developed numerous petechial hemorrhages of the skin, which would lead one to infer that in addition to dilatation there had also been actual capillary damage.

Doubtless you will all recall in your own experiences with severe infectious diseases, particularly pneumonia and typhoid fever, patients who have presented the picture of falling blood pressure, rapid pulse and collapse. Certainly, in many instances this serious complication is a manifestation of shock, and probably results from an increase in the vascular bed due to capillary damage. Confusion of this state with cardiac failure will result in misdirected and possibly harmful therapy. The importance of this point of view was pointed out by Theodore Janeway in the *New York State Medical Journal* for 1907, when he wrote on "Some Common Misconceptions in the Pathological Physiology of the Circulation and Their Practical Significance." He said, "We must in most cases abandon the idea of cardiac death at the height of acute infectious diseases such as pneumonia, typhoid fever and septic fevers. . . . In place of heart failure we must write vasomotor failure." The discussion of this complication of infectious disease in many modern textbooks of medicine offers a discouraging contrast to Dr. Janeway's enlightened attitude.

Up to this point we have dwelt upon the occurrence of shock in a variety of clinical conditions, stressing in each instance the mechanism which dominates the picture. In some of these situations shock resulted primarily from a rapid decrease in circulating blood volume, whereas in others the chief factor was vasodilatation. However, we think it is only fair to state that this is a diagrammatic visualization of processes which like other biological phenomena are more complex than we have seemed to indicate. For example, in histamine shock, although the primary disturbance is admittedly due to capillary dilatation, nevertheless capillary dilatation is almost

method, the intravenous injection of 50 cc. of 50 per cent glucose, which may be conveniently kept on hand, is of some temporary value, as it will draw fluid into the blood stream from the tissue spaces. Its action is fleeting and it should be followed promptly by the intravenous injection of 1000 to 2000 cc. of normal salt solution. This procedure may be repeated within two or three hours without any danger to the myocardium. The response of the blood pressure is the best indication for such repetition. The value of salt solution in the treatment of shock developing in the course of infectious diseases has not been thoroughly tested, and final conclusions as to its usefulness are still uncertain. In shock due to other causes, dramatic results follow this therapeutic measure.

The ideal treatment for shock is a large blood transfusion, and every patient likely to develop shock should have his blood grouped early in the course of his disease. When salt solution has failed, transfusion may turn the tide. The theoretical basis for the fact that blood is more effective than salt solution lies in the assumption that it contains a nondiffusible substance, *i. e.*, serum protein, which makes the influence of added blood a more permanent one. One cannot accept this suggestion without caution, for it has been clearly proved that in histamine shock whole serum leaves the blood stream; in other words, the capillaries become readily permeable to protein. However, there is no denying the greater therapeutic value of blood over all other fluids. In an attempt to find a substitute for blood, numerous colloidal substances have been tried. The most prominent of these is acacia. During the World War, this solution was tried and given up because of the severe reactions which frequently followed its administration. In the past two or three years, methods of preparation of acacia solutions have been improved, and while enthusiastic reports from its action have appeared, it is too early to recommend its general use.

All therapy in shock should be intravenous rather than subcutaneous or intramuscular. The rapidity of response is much greater when the intravenous route of administration is employed, because the poor peripheral circulation slows subcu-

induce shock without the aid of salt loss, dehydration or circulating toxin. In the field of internal medicine, it is recognized that one of the immediate effects of extensive infarction of the myocardium is a clinical picture of falling blood pressure and collapse, which is similar to, if not identical with shock. It is hard to believe that such a rapidly developing syndrome could result from tissue damage and it seems likely that it is brought about through a reflex nervous mechanism. Obviously, the development of shock in cardiac infarction is a fortunate physiologic disturbance and hence should not be treated as in other conditions.

Before proceeding to the discussion of therapy, we should like to enumerate briefly a few of the systemic effects of shock. The most significant effect is the interference with tissue function which results from circulatory stasis and diminished blood supply. No organ shows this disturbance more strikingly than does the kidney. Renal function is compromised and anuria frequently results. This, in turn, definitely upsets the acid base equilibrium of the body and in the case of diabetic shock prevents the excretion of ketone bodies, thus adding to the seriousness of the disease state. The tissues of the central nervous system are also included in the general damage and the resulting pathology doubtless plays a large part in the terminal stages.

The treatment of shock is more or less independent of its cause. Whether it be due to trauma, toxemia, hemorrhage or dehydration, the physiologic problem is the same; namely, a disparity between the circulating blood volume and the vascular bed. On one hand there is primarily a decreased blood volume from hemorrhage or fluid loss; on the other, an increased vascular bed resulting from capillary dilatation. The need for immediate measures to increase the circulating blood volume is common to all types.

We think it is reasonable to say that the longer the state of shock is permitted to exist, the more difficult it becomes to alleviate it and the higher is the mortality. Consequently, delay in initiating therapy is dangerous. As an emergency

taneous absorption tremendously. This applies to hypodermic medication as well as to fluid administration.

The use of vasoconstrictors, such as epinephrine, is not helpful and may, indeed, be dangerous. From a physiologic standpoint they are contraindicated because the blood vessels which they affect are already constricted to the disadvantage of the capillary circulation, as has been shown by studies of both the skin and visceral arterioles. There has been much mention of heat loss as a contributing cause of shock and it is consequently essential to keep the patient as warm as possible.

In conclusion it should be stated that while most of the material presented is an old story, we feel that it is a story worth retelling because there is no doubt that the importance of the state of shock, particularly as it occurs in the field of internal medicine, has not received its just and proper emphasis

into the emergency clinic with their burns dressed with oil or ointment applied by some general practitioner who has given first-aid. Because of this, it is of value to review the problems involved in handling severe burns, describe the method used in the application of tannic acid and outline a way in which it may become a standard first-aid remedy.

In order to understand clearly the rationale for this treatment, it may be well at this point to review briefly the pathology of burns of different degrees. Although we are primarily concerned with second and third degree burns, it will make the picture more complete to include the first degree lesions, as they represent the early stage of the deeper burns.

The primary response of tissue to intense heat manifests itself by erythema which histologically shows capillary dilatation, edema and polymorphonuclear infiltration beneath the skin. If the heat is continued, the second degree stage is reached and a superficial coagulation necrosis takes place, forming a blister between the superficial and deep layers of the skin in which fluid accumulates. The third degree burns show a necrosis which goes through the subcutaneous tissue and may involve even the muscle. Adjacent to the burned area, there appears a margin of edema and under the microscope there can be seen a sharp line of demarcation between the burned and the living tissue. This margin is made up largely of phagocytic cells, extravasated red cells from the damaged capillaries, and necrotic tissue. The necrotic surface of the burn gives off a serous exudate and it is through this constant seepage that a large amount of body fluid is lost.

Immediately following a bad burn the patient gives the clinical picture of severe shock accompanied by a loss of body heat and intense pain. The pain is increased if cold air touches the burned surfaces. The preliminary shock must be treated with morphine, with heat applied to increase body temperature and with adequate covering to protect the burned surfaces from the air. If the patient is in severe shock, no attempt should be made to treat the local lesions, as any surgical procedure at this time might prove fatal. Warm blankets and hot water

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THE TREATMENT OF EXTENSIVE BURNS¹

FEW households are equipped to deal adequately with severe burns. The average family medicine chest contains a first-aid kit, iodine, boric solution, cough medicine, gargles, cathartics, aspirin and soda bicarbonate; but aside from a possible tube of unguentine, there is no specific burn medicine which can be called on in an emergency. First-aid courses have taught the slogan: "Send for the doctor and treat the shock"; and this advice is followed meticulously in the majority of cases. Certainly no layman would consider trying to set a fracture or tie off a bleeding vessel, but burns are different. Because of the pain that ensues, all sorts of home remedies are immediately brought out, and oil, butter, lard or the never-to-be-left-out carron oil are smeared over the burned areas. This only hinders later treatment; and in place of oil or grease, warm blankets or complete submersion in a tub of warm water would be equally comfortable and infinitely less harmful.

If the burn involves only a small area on the hand or arm, as is often the case, it is advisable to prick the blister, release the fluid and strap the dead skin down tight with adhesive. Often when treated in this way, the dead skin around the margin becomes adherent again and leaves only a small central area to be epithelialized. It is in the extensive burns that a very serious problem is met. It is only in recent years that tannic acid has provided a very satisfactory means of dealing with them.

Much has been written in the surgical journals about burns and how to treat them, but there are still many cases brought

¹ From the Service of F. W. Bancroft, M. D., Fifth Avenue Hospital.

stored, the patient is removed from the bath and dried, the burns are treated with a tannic acid spray and the body surface kept dry and warm with a hot air blower.

R. M. Penick, Jr., has reported the use of an aqueous solution gentian violet which he has used in place of tannic acid. It forms an eschar over the surface of the burn and has the added advantage of antiseptic properties. In this way, he feels that the danger of secondary infection is minimized.

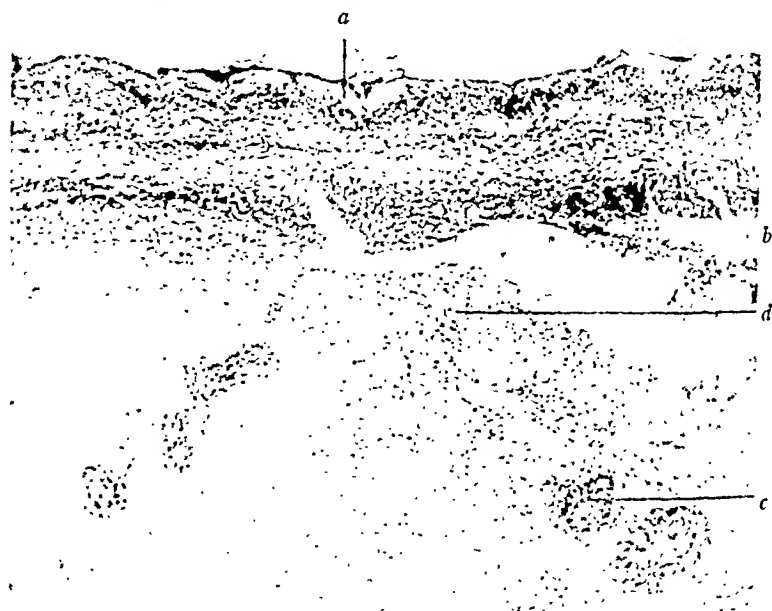


Fig. 242.—High power view of burn tissue treated with tannic acid. *a*. Tanned membrane; *b*, line of separation; *c*, hair follicle; *d*, subcutaneous connective tissue. (Bancroft, F. W. and Rogers, C. S., *Ann. of Surg.*, July, 1926. Published by J. B. Lippincott Co.)

This early period covering the first forty-eight hours is of greatest importance, as the mortality during this period is very great; probably shock and dehydration being the two most important factors. (Charts 1 and 2.)

During the first week or two following the burn, the patient suffers from what has been termed "toxemia." The temperature is elevated, and the kidneys show signs of impaired function. There has been much discussion as to the cause of this

bottles will keep the patient comfortable, and an infusion will help to restore fluid loss. If the patient is not in severe shock, the burned areas may be treated at once. The blisters should be opened, the dead skin excised and any loose bits of necrotic tissue removed from the surface. If oil or grease have been applied, this must be thoroughly cleaned off, as tannic acid will not coagulate tissue with a greasy coating. The skin around the burned areas should be cleansed with soap, water and benzine and dried with alcohol and ether in order to remove all dirt and bacteria which might later contaminate the burned fields. A 10 per cent solution of tannic acid may then be sprayed on the surfaces and the patient put under a cradle with a light which will keep the body warm and the burned areas dry. The solution may be sprayed on every half hour until a heavy black crust has developed; then the patient may be kept dry by exposure to warm air. The tannic acid coagulates the necrotic tissue and prevents absorption into the system of proteins produced by the burn. The membrane formed by the tannic acid is thick and leathery, it adheres to the normal skin around the margins and makes an air-tight covering which relieves pain and prevents fluid loss. Figure 242 shows the microscopical picture of a burned area treated with tannic acid. It is of particular interest in this plate to note the absence of infection under the tannic acid crust and the good condition of the subcutaneous tissues.

D. B. Wells of Hartford, Connecticut, has made a valuable suggestion for the treatment of very extensive burns, which is to place the patient immediately, clothes and all, into a bath of warm water containing a very dilute tannic acid solution. This relieves the primary shock by increasing body heat and it stops pain by protecting the burned areas from cold air and by the analgesic action of the dilute tannic acid. Clothing may be soaked off carefully while the patient lies in the water, and the skin removed from the blisters with a minimum of discomfort. The water can be changed from time to time to keep it warm and clean, and fresh tannic acid powder added. After the areas have been cleaned and the body heat has been re-

unable to reproduce the toxic symptoms. Harrison and Blalock reached the same conclusion as Kapsinow after repeating the experiment on dogs. Underhill, Kapsinow and Fish did some very interesting work on burned tissues which brought out the following facts: (1) That resorption of fluids from burned tissue was greatly diminished, (2) That the fluid present in the tissues around burns very closely resembled blood serum. (3) That the fluid loss from the blood was very great in burn cases, often reaching as high as 70 per cent of the total blood volume. (4) That this edema fluid was high in chlorides, while the blood chlorides were markedly diminished. From the foregoing they concluded that toxic products would have a good deal of difficulty in being absorbed into the system from burned tissue, and that a large part of the toxic symptoms was due to low blood chlorides and dehydration.

The Mayo Clinic, in a symposium on burns, put themselves on record as believing that this toxemia was not due to toxins, but to blood concentration and acidosis. In addition to this work on dehydration, there has been much done in regard to the injury of the adrenal glands in severe burns. Weiskoten and Bardeen report hemorrhage and focal necroses of the adrenals in fatal burn cases. Crema, working on guinea-pigs showed that there was a diminution of lipoids, lipoid phosphorus and cholesterin in the adrenals; and Hartmann has shown that there is an increase in the output of epinephrine immediately following the burn. Harris reported a case which, at autopsy, showed hemorrhages in both adrenal capsules. Certainly, when the symptoms found in adrenal insufficiency, and those following severe burns are compared, there is a great similarity. (Chart 3.) This idea is leading some of the

CHART 3

COMPARISON OF SYMPTOMS OF CORTX DEFICIENCY AND BURNS

Low Blood Chlorides
Anhydremia
High Hemoglobin
Low Blood Pressure
Duodenal Ulcer

CHART 1

MORTALITY RATES IN 114 CASES OF BURNS
FROM LINCOLN HOSPITAL, 1922

								Total
Decades.....	1	2	3	4	5	6	7	
Deaths occurring in 1-48 hours (shock).....	5	2	..	2 ²	1	0	1	11
Deaths resulting from toxemia and infection.....	3	2	2	3	10
Deaths probably attributable to other causes.....	1 ³	..	1 ⁴	2
Number of cases.....	8	4	3	5	2	0	1	
Percentage.....	34	17 ¹	13	13	8	0	4	
Deaths.....	23
Percentage mortality.....	20.1
Percentage mortality due to shock.....	10
Percentage mortality due to toxemia and infection.....	10.1

¹ Note the high mortality in the first decade.² Patient also had fractured skull (1 case).³ Lobar pneumonia and suppurative pleurisy.⁴ Lobar pneumonia and acute nephritis.

CHART 2

FIFTH AVENUE HOSPITAL SERIES FROM 1929-1933

	1					Total
Decades.....	under 5	5-10	2	3-4	5	
Number of cases.....	34	4	5	12	0	55
Deaths.....	6 ¹	0	0	0	0	66
Deaths in twenty-four hours.....	4	
Deaths in forty-eight hours.....	1	
Late deaths.....	1 ²	
Percentage mortality.....	10.9
Percentage mortality from shock.....	9.0
Percentage mortality from toxemia.....	1.9

¹ All deaths under five years.² Death due to jaundice and hemorrhagic enteritis.

toxemia. For many years it was thought that burned tissue contained toxic products called by some histamine; by others, toxoids; and that these were absorbed into the system, causing damage to the kidneys and liver. Robertson and Boyd, in 1923, did a series of experiments in which they found that if burned skin from one rabbit was grafted on to an unburned rabbit, toxemia developed in the latter. Also, whole citrate of blood from a burned child injected into a rabbit produced a toxemia. From this they concluded that some toxic substance was present in burned tissue which, on being absorbed, produced toxemia. The toxins were thought to be secondary proteoses. This work was repeated by Kapsinow, but he was

surrounding skin. In burns where hair follicles have been left and supply islands of epithelium on the granulating surface, complete epithelialization, in the absence of infection, may take place under the crusts, lifting them off spontaneously as the process becomes complete. If the burn is third degree and all the skin and subcutaneous tissues are destroyed, it will be necessary at the end of ten days or two weeks to soften the crusts with boric ointment or wet boric solution dressings, and remove them in order to apply skin grafts. With the first sign of infection under the tanned surface, the crusts should be soaked off, and some form of antiseptic applied (Fig. 243). A 1/5000 aqueous solution of acriflavine works very satisfactorily, but gentian violet has been found to be equally effective.

As soon as the infected surfaces are slough-free, skin grafts should be applied. Pinch grafts are used as a rule, because they can be applied quickly and, when necessary, with local anesthesia. If, however, the areas are large, Thiersch grafts cover more space and can be used in conjunction with the others. Small areas at a time are grafted, as these patients, especially children, should not be subjected to more than ten or fifteen minutes of a light gas anesthesia. Early epithelialization of these areas, especially if they are around joints, is essential in preventing thick scars and contracture.

If healing and epithelialization have been delayed, and chronic infection is present, a microscopical study of this granulating area will show a superficial layer of exuberant granulation, below this, a line of cellular infiltration, and next a layer of dense fibrous connective tissue. The longer this area stays unepithelialized, the thicker and denser this layer will become. As it increases in density, it becomes more avascular, and this avascularity makes it increasingly difficult for the advancing margin of epithelium to receive nourishment (Fig. 244).

In preparing to skin graft an area of this sort, it is customary to curet off the exuberant granulations which can be separated in a definite plane of cleavage. This leaves an apparently clean vascular surface which is high to place the grafts.

workers to feel that the symptoms of toxemia are due entirely to adrenal damage and dehydration. This question has not yet been answered fully, but whether the cause is toxins or dehydration, or adrenal injury, the treatment is the same. The blood volume must be increased and the chloride content of the blood restored.

Probably the most important treatment during this first week consists in giving the patient plenty of fluids and salt. Often this may be given by mouth, but if the patient begins to vomit, clyses or infusions must be immediately employed. Bettman suggests that 1000 cc. of normal saline be given daily for each 25 pounds of body weight. The tannic acid crusts do a great deal to prevent loss of fluids from the burned surfaces, but the loss of fluids from the edema in the tissues must be counteracted. All burn cases should be typed for transfusions as soon as they are admitted. Some member of the family can usually be found to act as donor. Almost weekly transfusions may be given, the amount of the transfusion averaging about 50 cc. in small children, and not more than 150 or 200 cc. in adults. Frequent small transfusions seem to give better results than occasional large ones.

When the patient is over the preliminary period of shock and toxemia, the doctor's troubles are not at an end. Infection of the burned areas is always possible, and must be constantly guarded against, as such infection produces a toxemia which is responsible for much of the late mortality. The skin around the burned areas must be kept meticulously clean. It is desirable to use ether, two or three times a day over this area. This not only cleans and sterilizes, but also dries the skin. Ointments are to be avoided as they at once soften the crusts and make an excellent medium for the growth of bacteria. As long as the crusts stay dry and clean, they should be left in place. They act as an excellent protection for the new epithelial cells which are growing out over the burned areas; and if an attempt is made to remove them before they become loosened themselves, much of the new epithelium will be destroyed, and a bleeding surface left which may become infected from the

for the grafts. Where the areas are small and the epithelium can grow out readily from the periphery, a type of dressing



Fig. 244.—Scar tissue beneath superficial granulations. (Bancroft, F. W. and Rogers, C. S., *Arch. Surg.*, May, 1928)

should be used which will not stick. If you study the margins of the granulating area under a magnifying glass, after cleaning and drying with ether, you will see a thin, transparent, dry.

However, attempts to graft this surface are usually unsuccessful, as the fibrous tissue layer prevents them from getting adequate nutrition. It is therefore necessary to excise this entire fibrous layer also before a good surface can be obtained



Fig. 243.—Area of infection occurring beneath tannic acid. *a*, Tanned membrane; *b*, separation zone, filled with polynuclear leukocytes; *c*, irregular zone of epithelium arising from hair follicle; *d*, capillary filled with numerous polymorphonuclear leukocytes, showing gradual spread of infection; *e*, infection proceeding downward along hair follicle. (Bancroft, F. W. and Rogers, C. S., Arch. Surg., May, 1928.)

Early epithelialization of burns around joints is essential in preventing contractures. The bad results usually occur when a patient lies for weeks with an arm or leg covered to great extent by open granulating surfaces. Unless the part is elevated, an extensive edema will develop which hinders the growth of the new epithelium. The heavy fibrous tissue base beneath the granulations increases the chances of contracture because as this base becomes more organized, it contracts and makes the tissues fixed and inflexible. Early grafting with its subsequent epithelialization of the burned area prevents the formation of the fibrous tissue base, and allows early motion of the extremity, thus preventing stiffness from disuse and contracture from heavy scar tissue.

In reviewing this subject, probably the most important points in the handling of burns is the emergency treatment. There is no reason why every household should not keep a package of tannic acid powder in the medicine chest. As the solution has to be made up fresh each time it is used, Bettman suggests that eight level teaspoons of the powder, dissolved in a glass of water, makes approximately a 5 per cent solution and could be applied to the less extensive areas. Also it would be on hand for the doctor to use on the more extensive lesions. Warm blankets or a warm bath provide the best first-aid until a doctor can be reached. Undoubtedly this treatment gives an extensive burn case an excellent chance for recovery; but something more than following a prescribed routine is needed. Serious cases require untiring watchfulness and care, on the part of the doctor, and the constant attendance of an experienced nurse to accomplish the desired result. No hard and fast rules can be set down to cover every phase of the treatment. Each case presents a separate picture, and the doctor must be ready at any moment to alter the treatment or change some part of the routine to meet successfully any special need which may arise.

I wish to express my thanks to Dr. F. W. Bancroft for the use of the microphotographs reprinted in this article.

pale bluish membrane extending outward from the normal skin. This represents a thin layer of epithelium. As this layer advances, it shrinks down the exuberant granulations ahead of it. If the granulations are kept free of bacteria and this advancing margin adequately protected, epithelialization will take place rapidly. A dressing of boric acid ointment covered with strips of adhesive may be used over the lesions. This dressing is changed every two or three days, and when removed, is floated off with benzine, thus avoiding disturbance of the new epithelium. Some physicians prefer wet boric acid dressings, but they must be kept constantly wet, and the gauze fine enough so that the granulation will not grow into the meshes.

One of the most important things to be considered during this period is the patient's general condition. After severe toxemia and fever, often of several weeks' duration, their general nutrition has suffered badly. Special attention should be given to the diet in an attempt to build up the patient. Cod liver oil or viosterol, fresh air and sun, either artificial or real, help very materially. Transfusions during this period, especially in the presence of infection, are of great benefit.

The other complications which must be looked for are hemorrhagic enteritis and bleeding duodenal ulcer. These conditions may occur fairly early in the course of the illness, and may prove fatal. Brandson and Hillsman found that the intra-abdominal temperature is raised with severe burns and may account for visceral lesions, ulcers occurring with abdominal burns, and severe toxemias when the burned area is in proximity to the spinal cord. However, the only case of hemorrhagic enteritis with burns which I have seen was in a child with burns around the head, neck and chest.

Endocrine upsets also occur and may link up with adrenal damage. A young girl was admitted to the Fifth Avenue Hospital with burns involving over two thirds of her body surface. During her convalescence, she went through a period of thyrotoxicosis, with tremor and exophthalmos, and for six to eight months had amenorrhea; but on recovery these symptoms cleared up entirely.

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purines, nitrites, acetylcholine. This kind of arterial reaction can be produced by barium salts. Spasm is always a pathologic process.

Like the muscle in the artery, the skeletal striated muscle possesses several kinds of reaction. Voluntary contraction and tonus are physiologic attributes. A third reaction is the painful cramp which probably corresponds to the spasm.

Insufficient blood supply to an active organ may develop in three ways: (1) By arterial spasm; (2) by failure of physiologic dilatation, and (3) by nonappearance of the increase of the circulating blood volume which normally and physiologically is obtained through evacuation of the blood depots in liver and spleen.

The blood depots, as Barcroft showed, are closed by contraction of the veins. The hepatic veins in dogs have a special muscular apparatus the contraction of which holds 1500 cc. of blood in the liver. This reserve of resting blood lying adjacent to the right auricle is suddenly evacuated if there is a greater demand for circulating blood, as in physical effort and in cold temperature. The opening of the hepatic veins is caused by stimulation of the sympathetic nervous system and therefore by adrenalin and similar drugs like ephedrine and neosynephrine. The contraction of the hepatic veins is increased during the hours of digestion, also by allergenes, and in the highest degree in anaphylactic shock.

The closure or the failure of the door veins of the blood depots to open is a spastic vessel reaction, a form of angiospasm closely related to one of its most interesting manifestations, namely angina pectoris.

Attacks of angina pectoris occur mostly during work and in cold temperature, particularly after meals during the hours of digestion. The mechanism seems to be very simple. The output of blood per minute increases 500 per cent (from 5 to 20-25 liter) during work, in cold temperatures about 200 per cent to about 20 liter. The O_2 consumption of the heart increases in proportion to the increased action. The less the output of blood per minute is carried by a higher beat-volume and not

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ANGIOSPASTIC DIATHESIS¹

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NORMAL or adequate function of the body and every organ or system depends upon the supply of blood. The total volume of blood is so small that increased action of *one* organ is not possible without change of the general distribution of the blood. An active organ needs more blood and receives it by dilatation of its vessels. In compensation vessels of other organs become contracted. The distribution of blood is governed by a regulating mechanism the exactness of which controls physiologic and pathologic processes.

The diameter of arteries may change by two different actions, *tonus* and *spasm*.

Tonus gives the arterial wall resistance to blood pressure and may lead to a certain degree of contraction but never to closure. Tonus is controlled by the central nervous system and affects all arteries simultaneously. It is absolutely painless and the patient is generally unconscious of it. The hypertonic vessel reacts in the regulation of blood supply on a higher level but usually in sufficient degree. This kind of reaction of the smooth arterial muscle can be produced experimentally in a pharmacological way by slow infusion of adrenalin solution. The hypertonus noticeable in the form of high blood pressure cannot be changed by drugs.

The other kind of reaction of the muscles of the arteries is the one known as *spasm*. Spasm is local, leads to a closure of the artery and to pain. It can be relieved by drugs like

¹ Address delivered Annual Scientific Day, Montefiore Hospital, Pittsburgh, Pa., November 25, 1933.

on the one hand, and circulation through the heart and muscle on the other hand. The spasmopathic sensitivity of the hepatic veins leads to an insufficient amount of circulating blood, to a painful dysharmony between action and circulation of the heart.

Because, as we mentioned above, the venous apparatus of the liver is sensitive to allergic conditions, we have to consider also the possibility of the allergic nature of angina pectoris. Later on we will show that allergic sensitiveness belongs to angiospastic diathesis. I have a typical case of allergic angina pectoris in mind. The patient was a man afflicted with migraine and complaining of attacks of angiospastic amaurosis. He suffered from severe angina pectoris when walking after a meal of beefmeat and beer.

The pathologic reactions of the closing apparatus of the liver, belonging to the spastic diathesis are, I believe, of the greatest clinical importance. There is no clinical literature as yet on the subject but I had the opportunity of studying a significant case.

A girl, five years of age, originating from a vasolabile family, having suffered from spasmodic acetonuric vomiting, took sick with high temperature, vomiting and extreme pallor. Enlargement of the spleen to a size not even surpassed by the size of the spleen in chronic myeloid leukemia and a considerable enlargement of the liver suddenly developed. There was no anemia in the usual sense, no diminution of hemoglobin and erythrocytes in volume, but a marked leukopenia (1600 to 2000 leukocytes).

Seeing this unusual picture and having in mind Barcroft's work on blood depots, I decided to identify this new condition and to name it Barcroft's disease. I assumed in this case an increased depot function of the liver and spleen and predicted a favorable outcome, with the possibility of several relapses. This prognosis came true. Up to the time this article was written eight attacks of the same type have taken place. With every attack the liver and spleen remained larger. It became evident that with the stimulation of the sympathetic system by

by a greater beat rate, the less O_2 will be needed. The heart can obtain more oxygen only by dilatation of the coronary arteries.

Attacks of angina pectoris can be caused by the three mechanisms mentioned above—by spasm of the coronary artery, by the nonappearance of the dilatation which is physiologic during increased action, by nonappearance of the increase of the circulating blood volume in work and in low temperatures. According to H. Rein, increased venous supply predisposes toward an increased volume of the single beat and also an increased output of blood per minute.

There are different views about pain in angina pectoris. According to H. H. Meyer, the extension of the wall of the arteries is the cause of the pain and not the contraction. In the case of arterial spasm stretching of the wall of the artery above the spastic part can be supposed. Hans Kohn believes that the muscle of the heart itself suffers in the form of a cramp. I agree with the opinion of Rothschild, that dysharmony between action and blood supply generally causes pain. The less blood, the less oxygen and the more stasis of CO_2 . Incomplete oxygenization induces splitting of carbohydrates, proteins and amino-acids, in turn producing formation and stasis of lactic acid and decrease of pH .

Every one of the three circumstances causing angina pectoris is identical with dysharmony between action and blood supply. That angina pectoris occurs in persons with angiospastic diathesis and even in an early age of life is no reason to assume that spasm of a coronary artery is the only basis of the attack.

Individuals with angiospastic diathesis are predisposed to pathologic closure of the veins of the liver and spleen. Enlargement of the liver and spleen during and after an attack of angina pectoris may frequently be found. The occurrence of angina pectoris during walking or working after a meal in cold air can be better understood from this point of view than in any other way. In this condition there is a competition for blood between the splanchnic system and particularly the liver

where is able to induce damage of tissue, beginning with transient swelling and ending with necrosis. In its effect on the heart, muscle, arteries and capillaries are endangered.

• After this review of a special but very important field of angiospastic disease we have to consider the constitutional picture of general angiospastic diathesis, more frequently found in females. These unfortunate persons could be and should be frequent visitors in the doctor's office, if physicians would have a better understanding of this condition.

The angiospastic diathesis is most commonly found in the asthenic type. The color of the face is usually pale and therefore the diagnosis of anemia is frequently and erroneously made. However, the color changes, the face appears smaller, the nose seems to be longer and deep shadows develop around the eyes. Cold feet, cold nose, cold and sometimes wet hands appear. This coldness may be noticed particularly when the patient goes to bed and keeps him from falling asleep. The individual has the subjective feeling of coldness, complains of cold shivers running down his spine and also complains regularly of migraine and all the various attributes of this angiospastic disease. The patient easily tires, feels exhausted after waking from sleep, which is often disturbed by bad dreams. He is anxious, uneasy and extremely sensitive to noises, odors and also to light, but especially to odors. These women elsewhere, in the street, hotel, car, train or boat will note everything disagreeable that would remain unnoticed by the normal person. They suffer from a variety of pains—pain in the neck and in the back, lumbago and sciatica. In going over the personal and family history, we find a diagnosis of rheumatism, urticaria, dermatographia, Quincke's edema, asthma, and quite regularly attacks of sneezing: in a word, the general symptoms of allergic hypersensitiveness.

Besides the arteries, the intestines show spastic reactions. The appetite varies but is mostly poor at breakfast. The tongue is coated. There is a bad taste in the mouth. These individuals frequently complain of pyrosis and a feeling of fullness after meals. The gastric juice shows hyperchlorhydria,

the injection of adrenalin and the administration of neo-syneprine by mouth, I was able to reduce the severity of the episodes. Between attacks the child was quite well.

In a number of cases the nonopening of the venous doors of the liver, *i. e.*, spasm plays a rôle in the occurrence of angina pectoris and is important also in the prophylaxis and therapy of this condition.

In therapy, besides the sympathicotropic substances, administration of atropin, heating of the liver and spleen by baking or, better still, by radiation with ultrashort waves are helpful. But of the greatest importance, especially in prophylaxis, is the fight against every kind of enlargement of the liver. The administration of small meals, always recommended by physicians and followed by patients, according to their own experience, may be mentioned from this point of view. Furthermore, the evacuation of the blood depots in the liver and spleen is aided by bodily exercise. Life without exercise not only weakens the heart muscle but relaxes the venous system of the liver and spleen.

Enlargement of the liver is induced after the age of forty by the weakness of the abdominal muscles and the diaphragm. Those persons who have a sense of fulness in the abdomen after meals and open the last button of the waistcoat in order to secure more comfort are exposed to enlargement of the liver and dilatation of its vessels with their consequences on the condition of the heart.

In this condition deep breathing with contracted abdominal walls is to be advised. By this procedure the blood content of the liver is reduced and the stream of blood from the liver to the right heart and also the flow of bile are increased. I believe that this simple exercise, when carried out frequently enough during the day, will protect against chronic enlargement and increased blood content of the liver and thus help to prevent this particular kind of angina pectoris.

We are dealing here with a functional pathologic condition, which takes place without any obvious anatomical lesion. But dysharmony between action and circulation always and every-

about their pains and disagreeable sensations. This spares the husband and her associates, but without any psychic help and relief by communication, the patient approaches a quicker breakdown.

Everyone is familiar with individuals of this kind. Here we are dealing with one of the most common pathologic conditions, unknown in the textbooks and medical schools. All of these symptoms and their reactions, or the majority of them, cannot be controlled by will or by good behavior. They belong to the involuntary autonomous system. They are functional but certainly not hysterical.

This angiospastic diathesis has to be recognized as a real clinical entity. We need the label not alone for the records. The patient himself requires a label for his particular disease. For his own understanding and to safeguard his position in the family from the suspicion of hysteria, exaggeration and affectation, as well as to safeguard the peace of the family, we need the sympathetic recognition by medical science of this unhappy condition. Thus we have the diagnosis "angiospastic diathesis."

From the basis of angiospasm, functional disease and anatomical damage originate. The most frequent disease is migraine. Important also are epilepsy, eclampsia and vertigo originating in the vestibular apparatus.

By a careful study of the history of patients suffering from arterial hypertension and genuine contracted kidney it becomes evident that migraine and angiospastic diathesis play a rôle in its etiology. This is also true for the hypertonic type of kidney disease in pregnancy.

Arterial spasm by degree induces arterial thrombosis.

The angiospastic diathesis opens a large field for therapy. In order to visualize the limits of our possibilities, we have to face the fact that constitutions cannot be changed. But the earlier in life the angiospastic diathesis is recognized, the better the results that treatment can give. Education, exercise, training and the choice of a profession are of the greatest importance. Here is a field for psychic analysis, not for the purpose

in consequence of which, at least in the hours of digestion, phosphaturia may appear.

Under such circumstances the acid base equilibrium is damaged or endangered. Sodium bicarbonate taken frequently in excessive and in continually increasing dosage raises neuromuscular irritability and should be substituted by calcium carbonate.

Loss of hair occurs periodically. Dermographia can be produced in all cases, sometimes of a particular type, so that the usual red stripe is bounded on every side by a white stripe, indicating the accompanying spasm or collapse of the capillaries in these zones.

In all cases of angiospastic diathesis a painful sensitiveness of certain zones in the muscles and of the abdominal aorta and the iliac arteries and hypersensitivity (E. Libman) can be found.

Suffering from complaints like these, which may vary from day to day, surrounded by a world which always produces disagreeable impressions and a feeling of fatigue, unable to go along with normal individuals, the patient's mind becomes more and more uneasy. He is not able to differentiate between great and small affairs. Everything seems to be difficult, every day brings its insoluble problems, and life appears difficult and menacing. As long as these women remain unmarried and under the influence of an understanding mother, the psychic picture may be less significant. But with the increase of duties after marriage, by the complete misunderstanding of the situation on the part of the husband—especially if he is of the opposite type, young, muscular and easy going—and by the still less understanding of a possible mother-in-law, the patient begins to fight against the weakness of her constitution. The fruitless desire to control the sensory, allergic and psychic irritability involves continuous overstrain and induces fatigue, unhappiness, mental explosions and tears. Some of these patients complain greatly about their various troubles. The result is often a diagnosis of hysteria. Another group of patients tire of complaining about themselves and stop speaking

of discovering sexual injuries, but to create an understanding of the world, particularly of the patient's world, to enable him to differentiate between important and unimportant matters, to avoid an unnecessary struggle and to be reconciled with everything unalterable. Angiospastic individuals can be fighters only at the cost of, and with harm to, their health and well-being.

Massage and hydrotherapy can be useful when administered with regard to the patient's increased irritability and fatigue. Cold applications do no good. Cold bathing and swimming do not produce the afterwarmth which normal people enjoy. On the contrary, freezing and shivering persists for a long time and are sometimes accompanied by blueness of the lips, nose and nails. A warm climate is beneficial. Bucky's Grenzstrahlen often produce excellent results in spastic conditions.

Control of spasms is possible by the use of drugs in the case of the arteries of the heart and brain by the administration of nitrites and purines. Spasm of the arteries of the legs (intermittent claudication) can be mitigated by quinine and aspirin.

Many individuals with angiospastic diathesis suffering from sleeplessness tolerate sedatives poorly, but a small dose of aspirin, pyramidon, etc., produces satisfying sleep. I am convinced that this statement is true, although it seems unbelievable. The antirheumatics produce dilatation of special arteries and also of the arteries of the midbrain, which is concerned with sleep.

A great number of so-called "vasodilating hormones" is advertised. I have seen no results except from acetylcholine, given by rectum or intramuscularly 50 to 300 mg. per day.

Against the general weakness and hypertonicity of the striated muscles administration of quinine and strychnine is useful.

Therapy may be and is indeed generally incomplete and not at all satisfying. Nevertheless, a physician understanding the condition and giving the patient the benefit of being understood with all his somatic and nervous troubles and social difficulties will be a great helper and healer.

SYMPOSIUM ON DISEASES OF THE PERIPHERAL VASCULAR SYSTEM

FROM THE VASCULAR SECTION OF THE DEPARTMENT OF MEDICINE, AND THE SERVICE OF DR. EDWARD PETERSON OF THE DEPARTMENT OF SURGERY, OF THE NEW YORK POST-GRADUATE MEDICAL SCHOOL OF COLUMBIA UNIVERSITY

The following clinics are included in this Symposium:

A. Wilbur Duryee: THE DIAGNOSIS OF DISEASES OF THE PERIPHERAL VASCULAR SYSTEM.

Irving Sherwood Wright: THE MODERN MEDICAL TREATMENT OF DISEASES OF THE PERIPHERAL VASCULAR SYSTEM.

Robert S. Ackerly: SURGICAL TREATMENT OF DISEASES OF THE PERIPHERAL VASCULAR SYSTEM.

Carl H. Greene: ARTERIOGRAPHY AS AN AID TO DIAGNOSIS IN DISEASES OF THE PERIPHERAL VASCULAR SYSTEM.

Dean A. Moffat: THE MODERN APPARATUS AND TECHNIC FOR THE STUDY OF DISEASES OF THE PERIPHERAL VASCULAR SYSTEM.

The treatment and the description of laboratory apparatus will be covered in other sections.

We shall devote most of our discussion to the arterial and capillary side of the blood supply, as it is here that the average clinician has the most difficulty in making a differential diagnosis.

The recognition and treatment of varicose veins, phlebitis and venous thromboses not complicating arterial disease are fairly well understood. Aside from these conditions there is very little pathology to discuss in regard to the venous channels except as these are involved to some degree in the various conditions we are about to describe.

The actual blood supply to an extremity is an ever-changing quantity, regulated to meet the existing conditions both locally and generally. For instance it may be increased to meet the demand for increased food to the muscles of that extremity or, on the other hand, as a means of disseminating heat that has been produced elsewhere in the body. It is only when supply is increased or decreased beyond these physiologic variations that we find signs and symptoms of vascular disease. These abnormal increases or decreases may be due to disturbances of the innervation of the blood vessels, especially the arterioles as shown in Raynaud's disease by Lewis,³ or to real organic occlusion as described by Buerger¹ in thrombo-angiitis obliterans. Furthermore we may have an overlapping of the two conditions with a spasm of collateral circulation added to organic change in major vessels.

Under vasomotor types we find Raynaud's, acrocyanosis, erythromelalgia and possibly the hypo- and hypertensive diseases.

Under organic types we find arteriosclerosis, thrombo-angiitis obliterans, thrombosis and embolism, arteritis (rheumatic or syphilitic), and aneurysm. One should however remember that the two general types overlap in most instances and the basis for considering a condition in either group should be the predominating factor present.

Some of the organic conditions mentioned are easily diag-

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THE DIAGNOSIS OF DISEASES OF THE PERIPHERAL VASCULAR SYSTEM

RAYNAUD's disease, acrocyanosis, erythromegalia, arteriosclerosis, thrombo-angiitis obliterans, embolism, aneurysm, arteritis, phlebitis, and varicosities present to many clinicians a problem of differentiation beyond their powers of solution. The reason for this formerly lay in the scanty information available concerning peripheral vascular disease and the evident confusion of these diseases by many of the earlier writers. Furthermore, the majority of articles deal with only one of these conditions with very little space devoted to a careful differential analysis. Raynaud,¹ in his original group of cases of the disease now bearing this name certainly included several cases of thrombo-angiitis obliterans and arteriosclerosis and it has only been by careful study that we have been able to differentiate clearly these conditions. In 1928, Brown and Allen,² in their monograph on thrombo-angiitis obliterans presented a most comprehensive section covering the diagnosis of vascular disease. Since that time considerable interest has been aroused in the subject and many articles dealing with clinical observations and technical investigation of these diseases have been published.

The purpose of this group of articles is to present, first, the various means at hand today, both clinical and technical, which will help to make an accurate diagnosis and, second, the various forms of treatment being used. I shall attempt to emphasize the underlying causes of the signs and symptoms of these diseases and the clinical method of studying them.

and even here a careful history and physical examination may be sufficient to make an accurate diagnosis. I have borrowed as a basis for my charts one included in Brown, Allen and Mahorner's monograph on thrombo-angiitis obliterans. It has been altered and added to in order to conform with our present studies. It has also been divided into two sections, the first dealing with the history and the second with the physical or laboratory findings.

I shall deviate a little from the usual method of presentation of this problem and discuss each fact and symptom of the history in relation to the various diseases to be differentiated instead of discussing each disease and the associated symptoms.

Sex is most important as thrombo-angiitis obliterans is almost never seen in females while Raynaud's disease and acrocyanosis are most common in females. Arteriosclerosis of the large vessels of the extremities, especially the lower, sufficient to produce symptoms is seldom seen in females. It is interesting to note that diseases in which vasospasm plays the main part are usually found in women while those with organic occlusion predominating occur in men.

Race may help in diagnosis only in cases of thrombo-angiitis obliterans. Statistics show it to be more common among Hebrews although it is found in all races. It may be that something in their diet or habits of living is responsible for thrombo-angiitis being called a disease of the Jewish race.

Age helps us differentiate between thrombo-angiitis obliterans and arteriosclerosis as the former seldom occurs after the age of forty-five. From this age upward we may expect sclerotic changes to be the basis of similar symptoms. Most of the vasomotor diseases manifest themselves early in life before stability is reached.

Constitution.—Raynaud's disease, erythromelalgia and acrocyanosis are usually found in the emotionally unstable and often in the so-called "inherited constitutional inferiority" type. These patients are apt to be of the asthenic build. Thrombo-angiitis obliterans may fit into this group, and less frequently arteriosclerosis. Generally speaking all arterial

nosed because of their association with other disease in the body. Arterial embolism, rheumatic or luetic arteritis, and arterial or arteriovenous aneurysm should not be overlooked because of their association with the primary disease present. Likewise secondary changes in the vascular system from cardiac disease such as polycythemia vera should be easily recog-

TABLE 1

HISTORY AND FACTS IN DIFFERENTIAL DIAGNOSIS OF PERIPHERAL VASCULAR DISEASE

	Thrombo-angiitis obliterans.	Arteriosclerosis.	Raynaud's disease.	Acrocyanosis.	Primary erythromelalgia.
Sex	Males, 99%.	Males, 90%.	Females, 95%.	Usually females.	Females, 70%.
Race	Any. Hebrews predominating.	Any.	Any.	Any.	Any.
Age	25-45.	55-85.	17-35.	Young adult life.	30-50.
Constitution	All types.	All types.	Asthenic emotional instability.	Asthenic emotional instability.	Sthenic.
Previous infections	Frequent.	Frequent.	No known relation.	Possible local relationship.	No known relation.
Tobacco	In large amounts.	Moderate.	Not frequent.	Not frequent.	Not frequent.
Rye bread	Frequent.	Occasional.	Occasional.		
Claudication	Usually present.	Usually present.	Absent.	Absent.	Absent.
Pain.	Present.	Usually present.	Rare.	Occasional.	Present.
Rest pain	Usually severe.	Occasionally mild.	Absent.	Absent.	Mild to severe.
Type of pain	Sharp and knife-like.	Aching.	Absent.	Absent.	Burning.
Site of lesion	Any extremity usually unilateral at one time.	Lower extremity often bilateral.	Bilateral frequently upper extremity.	Usually unilateral only one digit.	Usually bilateral frequently entire body.

nized. Here we are reminded of the fact that a complete examination must be done in all cases with complaints referable to the circulation of the extremities, as often a primary cause may be found elsewhere in the body.

The somewhat complicated, technical procedures described in another part of this series of papers should be necessary only in very early stages of the diseases about to be discussed,

tion pain and in thrombo-angiitis obliterans becomes the major complaint. In this condition it is severe and usually present on rest as well as exertion which may produce slight relief. It is sharp and stinging and differentiated from the pain of arteriosclerosis which is less common with rest and not particularly severe. The rest pain is usually limited to the gangren-

TABLE 2

PHYSICAL AND LABORATORY FINDINGS IN DIFFERENTIAL DIAGNOSIS OF
PERIPHERAL VASCULAR DISEASE

	Thrombo-angiitis obliterans.	Arteriosclerosis	Raynaud's disease.	Acrocyanosis.	Erythromelalgia.
Postural color changes	Excessive rubor on dependency. Excessive pallor on elevation.	Same.	None.	None.	None.
Effect of cold	Mild cyanosis pallor in 30%.	Slight cyanosis in 15-20%.	Pallor and cyanosis in all cases.	Cyanosis.	Never.
Gangrene	Common.	Common.	Rare.	Rare.	Never.
Types of ulcers	Moist inflamed discharging.	Usually dry.	Small punched out superficial.	Same.	None.
Arterial pulsation	Diminished to absent.	Diminished to absent.	Normal.	Normal.	Excessive.
Edema	Frequent.	Occasional.	Possible scleroderma.	Absent.	Absent.
Superficial phlebitis	30% of cases.	None.	None.	None.	None.
Temperature of extremity	Low.	Low.	Low.	Low with spasm high with relaxation.	High
Visualization of capillaries	Hazy dilated stasis.	Moth eaten small stasis.	Greatly dilated. Full in rubor stage—Stasis.	Large dilated usually stasis.	Huge grotesque sluggish flow.
Visualization of arteries	With contrast dye x-ray shows blockage.	Same plus arteriosclerotic plaques.	Negative.	Negative.	Negative

ous or pregangrenous areas with some radiation up the extremity. In erythromelalgia the pain is burning or there is a sensation of heat. Raynaud's disease is characterized by lack of pain and the presence of alternate numbness with pallor and redness with warmth and tingling.

The site of obstructive lesions is usually in the lower

vascular disease occurring before senescence (as perhaps most diseases) are more often found in this type.

Previous Disease.—Although attempts have been made to correlate the occurrence of peripheral vascular disease with various infections such as typhoid fever, typhus fever, focal infections, etc., conclusive evidence of such a relationship is lacking.

Tobacco may play a causative or contributing rôle in the etiology of thrombo-angiitis obliterans. Hankavy, J., Hebald, S., and Silbert, S.⁵ believe this to be the case. Most cases of this disease present a history of excessive use of tobacco, but frequently this excess begins with the onset of symptoms. The recent work of Maddock and Coller⁶ at Ann Arbor, Barker⁷ at the Mayo Clinic, and our group,⁸ proves rather conclusively that tobacco smoking in a high percentage of average normals produces a vasospasm with a drop in peripheral skin temperature, and a slowing or stoppage of the blood flow in the visible capillaries. This occurs also in cases of thrombo-angiitis obliterans and arteriosclerosis and must therefore be a factor in reducing the blood supply in the collateral circulation and an aggravator of symptoms if not a primary cause.

Rye bread (ergot) has been shown by Kaunitz⁹ to produce in animals a condition of thrombosis of the major arteries similar to that in thrombo-angiitis obliterans. Since much rye bread contains ergot we may here have an etiologic factor for thrombo-angiitis obliterans as most of these patients give a history of an excess amount of rye bread. We have also noted in several instances symptoms of Raynaud's disease in women taking some form of ergot.

Claudication is a frequent symptom only with diseases of an obstructive type such as arteriosclerosis and thrombo-angiitis obliterans. It is frequently a long-standing symptom and often attributed to an orthopedic defect. When a patient complains of inability to walk usual distances because of pain in calf or foot muscles, a careful investigation of the arterial supply must be made.

Pain of a continuous nature often accompanies *claudica-*

Other mild trophic changes may be present with any of the above-mentioned conditions.

Arterial pulsation is, of course, diminished to absent below the obstructive lesions. Careful palpation will usually reveal this, but the use of an oscillometer will give a more accurate indication of the degree and location of the obstruction. Both manual and instrumental tests may give false impressions, however, due to the spastic closure of major vessels above the zone of organic occlusion.

Edema is frequent in obstructive lesions, perhaps most often with thrombo-angiitis obliterans, and especially if the extremity is kept in a dependent position.

Atrophy of muscles where the condition is of long standing may be evident. Disuse and poor circulation are undoubtedly the major factors. This is especially true of arteriosclerosis and comparative measurements may prove this fact. Lack of hair growth or nail development are evidence of deficient vascular supply.

Superficial phlebitis is rarely associated with any arterial disease except thrombo-angiitis obliterans, with which it occurs in 30 per cent of the cases.

The temperature of the extremity is dependent on the blood supply to that part, and, in all arterial disease with limited supply, is low. In the spastic type it returns to normal or above with the release of spasm; and in the obstructive type constantly remains low, often staying close to the level of room temperature. In erythromelalgia we find excessive blood supply with a consistently high temperature. Skin thermometers of various types are described in this symposium, and are of utmost value in studying the ability of collateral circulation to supply an affected extremity. By determining the degree of temperature rise following paralysis of the sympathetic nervous system (Morton and Scott¹⁰) by nerve block, spinal cord or general anesthesia, or by shock treatment with intravenous typhoid (Allen and Brown²), an index of vasomotor activity can be established and an idea as to treatment or prognosis established.

part of the body. However, thrombo-angiitis obliterans frequently is found in the hands and is more apt to involve one extremity at a time. The functional diseases usually attack the body symmetrically involving both hands, both feet or all four at once. The upper extremities are more often involved than the lower perhaps due to their more constant exposure to cold.

The physical and laboratory data may be discussed in each of these diseases as was done with the important facts and symptoms of the history.

Color changes are important. In obstructive lesions we have rubor when the part is dependent, and pallor on elevation. The degree of change is in direct proportion to the amount of obstruction and the completeness of the collateral circulation. These changes are usually more pronounced in thrombo-angiitis obliterans due to the more rapid occlusion of the vessels and the lack of development of a good collateral circulation. Color changes as a result of cold are characteristic of Raynaud's disease. Exposure to cold gradually produces spasm, pallor and blueness; and heat gradually brings on a stage of rubor. These changes are usually symmetrical, both feet, both hands, or all four extremities being involved. Sudden exposure to extreme cold will often produce a stage of rubor followed after a long period by one of pallor. In acrocyanosis we have local cyanosis on a spasm basis usually unilateral, often limited to one digit and without known cause.

Gangrene develops when the lesion obstructs the major vessels so rapidly and so completely that sufficient collateral circulation cannot be established, or perhaps even obstructs the potential collateral circulation. As a result we find this most commonly in thrombo-angiitis obliterans; frequently in arteriosclerosis; and only rarely and superficially in Raynaud's disease. In the latter case the main vessels are not closed off, and only such areas as are supplied by small arterioles in frequent spasm show gangrene. The gangrenous ulcers of thrombo-angiitis obliterans are usually moist and inflamed, while those of arteriosclerosis are dry, and of Raynaud's disease are very superficial and punched out in appearance.

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The visualization of the capillaries gives one an opportunity to note the rate of blood flow, the number and character of functioning loops per unit field observed. In obstructive lesions we have a decreased number of loops, irregularly and grotesquely shaped and in some cases small with edema often obscuring the field. In the spastic type, as Raynaud's disease, we find huge dilated loops, the dilatation extending from the venous over to the arterial limb, packed with blood moving rapidly in the stage of rubor; and irregularly filled with blood in stasis during the spastic stage. In erythromelalgia we find many large dilated loops filled with sluggishly moving blood.

The visualization of the arteries can be done with direct x-ray exposure revealing the arteriosclerotic plaques so characteristic of arteriosclerosis, or by injecting a contrast medium such as many workers including Brooks¹¹ or Greene¹² have done. The latter method is useful in locating the main site of occlusion and the degree of arterial collateral circulation. Here again spasm of the major vessel may confuse the picture. A section of this symposium will deal with the technic of this procedure.

Summary and Conclusions.—I have attempted to outline without elaborate details the facts of importance in both the history and examination of a patient suspected of disease of the arterial supply to an extremity. It is hoped that with greater dissemination of this knowledge, earlier diagnosis of this group of diseases may be made and more effectual early treatment instituted, thus avoiding long periods of painful illness and unnecessary amputations.

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smoking of tobacco results in decreased peripheral circulation, as evidenced by a drop in surface temperature and a marked retardation in the capillary blood flow. This has occurred in over 80 per cent of the individuals tested, and, in the opinion of all investigators, constitutes an unequivocal indication against the use of tobacco by patients with peripheral vascular disease. In addition, Drs. Harkavy⁴ and Sulzberger⁵ have independently presented evidence of tobacco hypersensitivity in patients with thrombo-angiitis obliterans.

The local care of incipient peripheral vascular disease is of great importance. Cleanliness is essential, with careful bathing at least three times a week a requisite. Hydrous lanolin should be rubbed into the skin after each bath to prevent hardness with subsequent cracking. Shoes should be selected with great care as to fitting and softness of leather. They should be large enough to permit the use of one or two pairs of woolen socks to be worn in cold weather, since chilling may produce serious results. The affected parts must be spared all possible chance of injury, which includes unskilful corn-paring, minor surgery, etc.

All foci of infection should be removed. A warm climate during the winter months will often retard or prevent the onset of a gangrenous condition, especially the superficial gangrene of Raynaud's disease.

As a result of the change of attitude toward these conditions and of an increasing cooperation between the surgeon and the internist, many of these patients are today walking on feet which were at one time scheduled for amputation.

Treatment should have a two-fold aim: (1) Increase of circulation in the affected part, and (2) relief of pain. The following types of medical and surgical treatment have been instituted with that aim in view:

1. **Postural Exercises.**—This treatment, first suggested by Buerger, is widely used. One modification of it constitutes holding the extremity perpendicular to the bed one minute; then hanging it over the bed one minute, followed by two minutes in the horizontal position. This should be repeated

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THE MODERN MEDICAL TREATMENT OF DISEASES OF THE PERIPHERAL VASCULAR SYSTEM

A CONSIDERATION of the differential diagnosis of the more common peripheral vascular diseases has just been presented. The discussion of treatment will be limited to the group in which deficient circulation, either temporary or permanent, is the offending factor, such as: arteriosclerosis, thromboangiitis obliterans, Raynaud's disease and scleroderma. The classification of each case, wherever possible, into one of the above groups, is, needless to say, of great importance from the viewpoint of the expected course and the ultimate prognosis in *untreated cases*.

Of even greater importance in the consideration of treatment are two other factors, namely: (1) The relative parts played by spasm and organic changes in the production of the symptomatology present, and (2) the adequacy of the collateral circulation. The answers to these problems represent the hope that one may entertain for successful medical and surgical treatment and the prognosis of the *correctly treated patient*.

Prophylaxis is the most satisfactory treatment in these conditions. Careful inquiry into occupational factors, such as lead poisoning; into foods, such as rye bread, which might contain an appreciable amount of ergot; into habits, such as excessive tobacco smoking; into the use of drugs, such as ergot, and into diseases, such as diabetes mellitus, will enable the physician to eliminate these important exciting factors early in the course of the disease. Recent work of Maddock and Collier,¹ Barker,² and our own group,³ has shown that the

(1) The object of typhoid therapy should be to get the maximum temperature *without* chill. A rise in the mouth temperature of two or three degrees will produce very markedly increased blood supply in favorable cases.

(2) The vaccine should be carefully diluted to 100,000,000 to a cubic centimeter and the preservative diminished to the smallest amount commensurate with safety. Several serological houses have prepared vaccine for this purpose (Kirk, Lilly). Vaccine, it must be remembered, is a suspension, not a solution. The initial dosage should be between 10,000,000 and 20,000,000 and gradually increased to 100,000,000 to 200,000,000. When using vaccine of the ordinary strength, 2,500,000,000 to 3,000,000,000 to a cubic centimeter, one may be more than 100 per cent inaccurate. We believe that this factor of error has been responsible for many unpredicted chills and other untoward effects. We have had no difficulty since adopting the above procedure. About two injections should be given per week. We recommend that the patient be in the hospital for the first one or two, after which they come to the clinic, receive their injection, and go directly home. Several patients who had been unable to work for two years or more, and had even had several toes amputated, by means of this simple procedure, have been restored to work for one to three years without further trouble.

(b) For patients in whom the use of typhoid vaccine might be accompanied by some risk, such as in advanced arteriosclerosis, and for patients suffering from almost purely spastic conditions, the *sterile milk preparations* intramuscularly have been helpful in restoring the circulation.

(c) The immediate effects of the above preparations are maintained for only a few hours, although permanent help does seem to be the ultimate result. In an endeavor to obtain a substance producing a prolonged immediate effect, the use of a *2 per cent suspension of sulphur in olive oil* has been studied by Mackay,⁶ Schroeder,⁷ Waller and Allen,⁸ and others. This dose is administered intragluteally, beginning with 1 cc. dosage, and gradually increasing up to 10 cc. (injected at one time).

for three fifteen-minute periods daily. It is especially helpful for the patients with organic occlusion of the deep vessels.

2. Fluids Intraduodenally and Intravenously.—For this purpose, Ringer's solution, sodium chloride, sodium citrate, etc., have been used. As a result of clinical and experimental studies, the use of these solutions has been abandoned at some of the leading clinics of the country. We have seen no evidence of true merit in this procedure. Silbert, Samuels and their coworkers continue to advocate the use of hypertonic (3 to 5 per cent) sodium chloride intravenously.

3. Radiant Heat.—Use of a carbon filament lamp and diathermy may be helpful in increasing local circulation. Diathermy must be used with extreme care and skill in such cases, since, with subnormal circulation, a burn may be extremely dangerous.

4. We are convinced that hot and cold contrast baths are of value in a high percentage of these cases. Using two deep and wide containers, so that both arms or feet may be immersed to the elbows (or knees), the patient alternates, immersing the extremities for from one to three minutes in each, up to twenty-one minutes. The temperature of the cool water should be 40° to 50° F., and that of the warm water, 100° to 110° F. The last immersion should be in hot water. This should be repeated once or twice a day. This treatment is of value in both organic cases (collaterals) and spastic. Occasionally, in an individual instance, it is too painful.

5. Nonspecific proteins and allied substances have been of established value on both experimental and clinical grounds.

(a) Typhoid vaccine, intravenously, may be so used that there is a marked increase in capillary activity, with resultant increased blood supply, without untoward effects. The most suitable patients are those in whom spasm plays some part. Its use has been questioned in arteriosclerosis, but our results have been encouraging, and we have had no unfortunate occurrences. In these patients, the dilatation must occur in the collateral vessels. *The following principles should be observed:*

ized and released on the market, under the title, "Tissue Extract, 568" (Sharp and Dohme). Injections, beginning with 1 cc. and increasing to 3 cc. (30 units) every two or three days intragluteally have lengthened the time of activity necessary to produce claudication in the majority of the patients on whom it has been used. There is a slight temporary local pain at the site of the injection but no other untoward effects. There have been no chills, fever, or other systemic reactions noted. No definite effect has been noted on pain of other types, such as rest pain.

Its exact action is not known. Wolffe has noted that 250 mg. of adenosin phosphoric acid corresponded in activity with 1 cc. of this tissue extract. What the relationship of this finding to incomplete metabolism in the muscles may be has not been established as yet.

We have here a substance which is safe to use and has a markedly favorable effect on the pain of intermittent claudication in certain patients. Further work will be necessary to evaluate its use in other conditions.

Roth, Barker and Brown¹⁰ have recently reported their experience with this preparation. Our results have been favorable in somewhat lower percentages of patients than the figures quoted by the Mayo group.

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SURGICAL TREATMENT OF DISEASES OF THE PERIPHERAL VASCULAR SYSTEM

THE subject of this section of the symposium is not new but because of comparatively recent developments in the surgical treatment of Raynaud's disease and thrombo-angiitis obliterans and because of several new and ingenious tests of arterial spasm it has been gaining prominence during the past few years.

The cervicothoracic ganglion was resected by Jonnesco,¹ in 1896, for epilepsy and exophthalmic goiter. In 1899 Jaboulay performed a periarterial sympathectomy to relieve vasomotor spasm in an extremity. Jonnesco, in 1906, removed the inferior cervical ganglion and benefited a case of angina pectoris. Leriche, in 1913, popularized the operation, periarterial sympathectomy, and Bruening, in 1923, resected the cervicothoracic ganglion for Raynaud's disease and scleroderma. A new day in the surgery of the vascular diseases dawned as Royle led the way for the new operative treatment of Raynaud's disease and thrombo-angiitis obliterans. In 1924 he noticed how palpably warmer the extremity was after having a ganglionectomy for spastic paralysis on that side. Adson, in 1925, on a similar case, made the same observations and measured the increase in skin temperature. When he had proved that the skin temperature remained elevated for several months he thought there was justification for performing a sympathetic ganglionectomy on a patient suffering with Raynaud's disease. He operated the case on March 19, 1925, and the patient was greatly improved because his legs and feet became warm and dry, the color turned a normal pink and the pain disappeared. Diez with the same idea, on July 24, 1924, removed the lumbar

sympathetic ganglia and trunk to cure trophic and gangrenous lesions on a lower extremity.

After the year 1925, research progressed rapidly. The operation was used on a case of thrombo-angiitis obliterans with a successful result. This was interpreted to mean that there had been present with the organic occlusion a considerable amount of spasm. Other cases of Buerger's disease that were operated were not improved and they conversely were thought not to have had spasm. It was extremely important, therefore, to have proof of an existing vasospasticity in a case before resorting to surgery. In a case of thrombo-angiitis obliterans with an accompanying vasospasm, if the spastic element in the arterial occlusion is very slight its release will not markedly improve the impaired circulation but if the spastic element is considerable, in spite of an accompanying thrombosis, its release may increase the arterial flow enough to relieve pain, improve color and heal ulcers. The varying degree of functional and organic occlusion can be appreciated in a study of Wright's² chart.

Standard tests of the degree of spasm present in a given case were soon discovered. At first intravenous typhoid vaccine was used as an indicator of what might be expected from sympathetic ganglionectomy. Later, acetylcholine given intramuscularly and observed clinically served as a test of spasm. Spinal and general anesthesia, brachial and local nerve blocks followed by skin temperature readings now play an important part in determining the advisability of operation. After the injection of typhoid vaccine or acetylcholine, the indications for sympathetic ganglionectomy are, assuming that the patient is disabled: (1) Improved color, (2) increased warmth. (3) healing of ulcers, (4) relief of pain.

We have used typhoid vaccine not only as a test but also as a therapeutic measure and the following is the case history of a patient with thrombo-angiitis obliterans completely relieved for more than two years.

Case I.—An Irishman, forty-two years of age, gave a history of having injured his right first toe. From a slight abrasion a gangrenous ulcer formed

and finally a surgeon amputated the toe at its interphalangeal joint. The stump failed to heal and an ulcer formed spontaneously on the tip of the fifth toe of the same foot. Both toes were exquisitely sensitive to touch and pained whether at rest or with exercise. Elevation of the foot caused excruciating pain so that he had little rest at night. He smoked moderately and ate rye bread occasionally. The patient came under our supervision about eight months after his toe had been amputated. The use of tobacco was stopped. He was given hypertonic saline intravenously, local diathermy treatments, Buerger's postural exercises, and contrast baths for several weeks without the slightest improvement. The terminal phalanx of the fifth toe protruded through atrophic flesh. Intravenous typhoid vaccine was given one day and repeated three days later. Immediately after the second injection there was a cessation of pain in the toes. The pain never returned. The foot became warmer, the color improved, the gangrenous areas healed and the patient put on a shoe and returned to work. He has not had a recurrence in over two years. Vaccine was continued twice a week for six months, then discontinued. Dosage is discussed elsewhere in this symposium.

In this case there was an indication for surgery but by increasing the doses of typhoid vaccine an equally favorable result was obtained. Cures like this made us slow to adopt surgery. Although dorsal sympathectomy is not an extremely difficult operation it is a delicate one and carries the ordinary risks of anesthesia and shock. It is sufficiently drastic to cause a surgeon to weigh carefully the benefits gained by operation against the disability of the disease unoperated as suggested by Morton and Scott.³ Though drastic, the operation is conservative when compared with a painful prolonged illness, financial ruin and at last an amputation.

In the case of a patient who has a painful, occlusive arterial lesion which responds to vaccine therapy, but recurs if treatment is stopped; a patient to whom it is important to be relieved of endless visits for injections and who desires an operation for more permanent relief, a ganglionectomy may be advised if there is a rise of skin temperature of 10° F. following a local nerve block or a spinal anesthetic or a general anesthetic. If the elevation of temperature is less than 8° F. the result is apt to be unsatisfactory. Fingers can be infiltrated subcutaneously at their base most easily and the rise of temperature measured at once. Spinal anesthetics are given low and in small amounts without shock. Brachial nerve

March 25, 1933, by Dr. Edward W. Peterson, New York Post-Graduate Hospital, and an immediate amelioration of symptoms in the right hand was noted. The skin temperature rose 7° F., and the pain and sensitiveness left the hand. A slight Horner's syndrome was noted. One month later the patient, delighted with the result, requested that the left side be operated. This operation was performed April 27, 1933, and the immediate results were equally favorable. The patient was confined to bed for many weeks as a result of a lung condition which was not caused by injury to the pleura at operation. For six months the patient's hands have been free from pain and her skin temperature readings normal. The patient returned on November 21, 1933, because for one week she has had pain in the third finger of the right hand. On examination she was found completely free from pain in both hands with the exception of a paronychium $\frac{1}{2}$ cm. in length along the medial edge of the nail on the right third finger. At this point a small drop of pus welled out when the horny layer of skin was pricked—this infection was unrelated to her vascular condition. Both hands felt warm, dry and not sensitive to touch. The skin temperature readings were as follows: Right hand, thumb 84° F; first, second and third fingers, 86° F; fourth finger, 83.5° F. Left hand, thumb, 91.5° F.; first and second fingers, 84.5° F.; third and fourth fingers, 83.5° F. These temperatures are from 9° to 12° F. higher than before operation. The Horner's syndrome was hardly perceptible and both operative scars were fading. The patient was gratified with the results obtained. She has definite signs and symptoms of Raynaud's disease in both lower extremities and this will be treated medically for a few months of trial before surgery is recommended.

Because our results with dorsal ganglionectomy for Raynaud's disease and lumbar sympathectomy for Hirschsprung's disease have been favorable, we do not share Robertson's⁹ pessimism over the results of dorsal sympathectomy for upper extremity Raynaud's disease. He feels that the early good results obtained by operation will not be permanent but that all the old symptoms will recur after some months in spite of the selection of cases or the type of operation performed. Oughterson, Harvey and Richter¹⁰ find that after removing the second, third, fourth and fifth lumbar ganglia for lower extremity Raynaud's disease, a relapse may occur. Their patient had return of symptoms and a posterior nerve block elevated the skin temperature exactly as it did before operation. Observations will continue to be made on the unsuccessful cases and they emphasize the necessity of bringing together all of the data relating to the various types of treatment. Reid's¹¹ régime should be subscribed to by all. It is sum-

out that acute localized arteritis due to bacterial toxin or chemical substances frequently results in thrombus formation especially if the inflammation progresses slowly. In this case the chemical was probably chlorine. The patient was given typhoid vaccine intravenously to ascertain the presence of an accompanying spasm that might be relieved. After one month of injections once or twice a week the radial pulse quite abruptly disappeared and pain increased. There followed during the next two months a gradual formation of a solid cord along the course of the pulseless radial artery. Just above the cord a pulsation was felt. The thrombus ascended steadily. The daily rise was easily discernible. The pulsation of the artery just above the thrombus rose higher each day and when there was no longer pulsation in the axilla, operation was undertaken.

Operation: A small slit was made in the brachial artery in the upper third of the arm. The artery was dry but with a milking motion upward from the wrist, several inches of soft mushy thrombus was forced out under the pressure of the finger. The same maneuver applied from above downward on the axillary artery aided by the pulsation of the heart, forced the thrombus out with a rush of blood. The artery was clamped and about 1 inch of it was removed as a pathologic specimen.

Section showed a thickened intima, obliteration of the lumen, newly formed blood vessels, and inflammation. "Obliterating thrombo-arteritis." Clinically it was thought not to be the syndrome known as Buerger's disease although the pathologic findings were similar.

No attempt was made to anastomose the artery and reestablish circulation. The cut ends were separately ligated. Postoperatively the arm was kept warm with a lamp. The color improved, the pain subsided and the gangrenous areas became covered with new tissue. There was general improvement. The operation was delayed until the arm had developed considerable collateral circulation. We feel that the total excision of a section of the principal artery of the arm is coincidentally a sympathectomy and is, according to Morton and Scott,² of value in aiding the establishment of collateral circulation by the removal of sympathetic influences.

In our comparatively meager experience with ganglionectomy and ramisectomy we have had only encouraging results, as seen in the following case:

Case III.—The patient, a woman, twenty-three years of age, was studied and treated medically for one year. Her complaint was pain and numbness in both hands. Color changes due to heat and cold were marked but there was no color change with elevation or dependency. Skin temperature of the hands was 75° F. The capillaries when visualized by Duryee's and Wright's⁷ technic showed marked slowing of the circulation. The radial arteries were palpable but there was impending gangrene. The test for spasm with general anesthesia did not show an altogether favorable rise of skin temperature but a brachial nerve block gave an elevation of 9° F. in the upper extremities and a ganglionectomy was advised. A right thoracic sympathectomy was performed

twisted off and the proximal bit of the terminal phalanx was removed by a curet leaving sufficient soft parts for closure. Although the hemoglobin was brought down from 150 per cent to 95 per cent and the red blood cells from 8,000,000 to 4,750,000 the toe did not heal completely. Finally, it was apparent that the articular surface had sequestered and when the thin shell of articular cartilage was removed healing followed at once and all pain subsided in the toe. An amputation performed near a joint is likely to result in sequestration of the articular cartilage and in selected cases the removal of the cartilage at once might be advisable to prevent pain and delay in healing.

Arteriograms are helpful in determining the level of occlusion but generally it is wise to go high at the first operation to obviate the need of second amputation for failure of a stump to heal. Stumps above the knee make the most satisfactory stump to use with artificial limbs and there is no point to the sentimental attitude of saving all of the leg possible. As Eliason¹³ states it: (1) Multiple operations increase the mortality; (2) it is hopeless to amputate a foot or leg when the arteries immediately above it are incapable of supplying good circulation; (3) from an economic standpoint, high, early amputation is his choice.

ANATOMY OF SYMPATHETIC NERVOUS SYSTEM

On either side of the spinal cord throughout its length lie the ganglia and trunks of the sympathetic nervous system. Each spinal nerve has attachment to the sympathetic trunk of its own side by one or more gray rami communicantes. The thoracic and upper lumbar nerves are also connected with the sympathetic chain by white rami. The cervical, lower lumbar and sacral nerves receive only gray rami. Physiologic experiments have shown that visceral efferent preganglionic fibers arise from nerve cells in the gray matter of the spinal cord, pass out by way of the anterior roots, enter the white rami and thus into sympathetic chain. These fibers go up or down and eventually end around sympathetic nerve cells in some ganglion

marized as follows: Keep the skin warm and greased, prevent seams and wrinkles in the stockings from grooving the skin of the feet, advise large shoes to prevent pinching, rest in bed if an ulcer appears, assume the optimum posture of an extremity in bed to aid both the arterial and venous pressure, drink 3 quarts of water daily, exercise properly, give thyroid gland if indicated by basal metabolism, prohibit the use of tobacco, eradicate foci of infection.

Carter¹² feels that any procedure that prevents the cooling effect on the skin of evaporation of moisture whether the moisture be perspiration or a badly used wet dressing will aid in the prevention and the cure of Raynaud's disease. The casual application of a thermocouple to the extremity of a patient being treated by wet dressings at room temperature shows that the part so treated is 6 or 8 degrees cooler than the opposite extremity. The modality in the treatment of gangrene should be dry heat and if wet dressings are to be used for infections the warm soak with subsequent drying will not cool the part and thus aggravate an already deficient vascular condition. It is not unlikely that some of the chemical preparations used locally on ulcers may have undesirable effects upon the capillaries of the area under treatment. A bland ointment should be used unless the action of other preparations are known. Johnson, Scupham and Gilbert⁵ think that the favorable results of sympathectomy that are seen come from the fact that sweating is stopped, thus cooling of the part by evaporation is minimized. In cases of gangrene due to Buerger's disease, arteriosclerosis, diabetes or frost-bite Eliason points that wet dressings convert the relatively safe dry gangrene into an exceedingly dangerous moist, infected gangrene which may require immediate amputation.

The problem of amputation still demands our attention because of diabetic and arteriosclerotic gangrene and the cases of thrombo-angiitis obliterans that are totally organic in character. We have recently had a patient with polycythemia vera whose second toe on the right foot became mummified with a dry gangrene. The terminal phalanx was simply

not find it necessary to remove the inferior cervical ganglion to cure Raynaud's disease. They report successful operations in which only the second and third dorsal ganglia were removed and a Horner's syndrome averted. In practice, however, the ganglia often fuse in various ways. The inferior cervical may fuse with the first thoracic ganglion or the first and second thoracic may fuse. This adds to the confusion in the identification of the ganglia actually removed.

SURGICAL TECHNIC FOR THE REMOVAL OF THE LUMBAR GANGLIA

Peterson¹⁵ uses the technic essentially as it is described by Adson.¹ The approach is anterior through a midline incision. With the patient in Trendelenburg position and the intestines packed off upward the operation is done on the left or right side by incising the posterior peritoneum and elevating the structures necessary to expose the sympathetic ganglia as they lie near the aorta, on the lumbar vertebrae just mesial to the psoas muscle. The second, third and fourth lumbar ganglia are removed and the sympathetic trunk is cut above and below the ganglia and all the gray and white rami are cut away. The operation has proved more effective in the treatment of Raynaud's disease of the lower extremities than dorsal sympathectomy for the upper extremities. Peterson reports 3 cases of Hirschsprung's disease in which the operation has caused complete three-year cures in children.

Reference has previously been made to the work of Swift and Flothow⁴ in which they inject the sympathetic ganglia directly. It is thought by some that this fine technic may replace the operative procedure completely. The authors state that the injection of novocaine as an indicator that certain pain is sympathetic in origin preliminary to doing a surgical extirpation of the ganglia, is rational and simple. They do not think that alcohol injection of the ganglia is capable of replacing surgery in general treatment because of the difficulty in localizing the procedure. There is considerable risk in the

other than the first entered. From the latter nerve cells, the pain is continued by axons known as postganglionic fibers. The gray rami communicantes are made up of postganglionic fibers which pass from the sympathetic ganglia into the spinal nerve for distribution to blood vessels, glands and smooth muscle. In the white rami there are also visceral afferent fibers which are sensory sympathetic nerves carrying pain impulses to the spinal cord by way of the spinal ganglia and posterior roots. Phylogenetically speaking, the first formed, primitive human sympathetic nervous system is found in the walls of blood vessels and intestines. The autonomic nervous system can and does act independently of its more obvious control mechanism, the sympathetic ganglia and the brain. This is particularly noticed when the arc is cut and regeneration cannot occur. While these nerves function, total abolition of vasospasm cannot be attained.

SURGICAL TECHNIC FOR THE REMOVAL OF THE UPPER THORACIC GANGLIA

We have used the posterior approach described by White.¹⁴ The skin incision is oblique in the region of the transverse process of the second thoracic vertebra. The trapezius, rhomboid and serratus posterior muscles are split in the direction of their fibers. The erector spina muscles are encountered and dissected off to expose the transverse process and the second rib. The transverse process and about $1\frac{1}{2}$ inches of the rib are cut away. The pleura bulges upward and is pushed down out of the field. The spinal nerves are in view and the sympathetic chain is found lying close to the body of the vertebra. Usually one does not know immediately which ganglion is in view, and therefore removal of everything possible through the incision described is practiced. This will include the inferior cervical ganglion in some cases, the first, second and third thoracic ganglia in other instances, together with their intervening trunks and all the gray and white rami communicantes in sight. With the removal of the inferior cervical ganglion the patient exhibits a Horner's syndrome. Swift and Flothow⁴ do

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injection and there is evidence that the sympathetics regenerate after their destruction with alcohol.

SUMMARY

1. In arterial occlusions there is either spasm or organic lesion or a combination of both.

2. The use of typhoid vaccine, acetylcholine, local nerve blocks, spinal and general anesthesia followed by skin temperature readings or a reading of blood volume with a plethysmograph constitute the best tests of spasm.

3. Intelligent basic treatment, with special emphasis on prevention of evaporation of moisture, is essential in the prophylactic treatment and final cure of some vascular diseases.

4. A thorough trial treatment with a vasodilating or a fever-producing substance should be given in the cases that show spasm of the blood vessels.

5. Thrombi, emboli and massive gangrene should be treated as special entities as they appear in the individual case.

6. Thoracic and lumbar sympathetic ganglionectomy and ramisectomy have given many "cures" in selected cases. They have, therefore, firmly established themselves and offer great hope to many victims of vascular diseases.

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arteriography has not yet been developed. Iodized oils, solutions of sodium iodide or other inorganic iodides, and strontium bromide have all been used. The oils have not been popular because of the danger of embolism. Solutions of iodides or bromides in concentrations sufficient to give satisfactory roentgenograms are painful and irritating to the intima so that



Fig 245.—Thrombo-angiitis obliterans with gangrene of big toe. Arteriogram reveals occlusion of the dorsalis pedis artery as well as one of the inferior branches of the plantar arch

there is danger of gangrene from their use. Recently a series of organic compounds containing iodine—uroselectan, skiodan, neoskiodan, and abrodil—have been introduced for intravenous urography. These latter compounds are more satisfactory arteriographic media than solutions of sodium or potassium iodide but are subject to the same objections.

While not ideal, the most satisfactory substance for routine

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ARTERIOGRAPHY AS AN AID TO DIAGNOSIS IN DISEASES OF THE PERIPHERAL VASCULAR SYSTEM

THE use of various methods of examination in the study of diseases of the peripheral vascular system has been discussed in other papers of this symposium. Palpation of the vessels, the presence or absence of rubor or cyanosis, oscillometric readings, microscopy of the capillaries, changes in the skin temperature, the histamine flare, the speed of the pulse wave, the velocity of the blood flow, and the effects produced by nerve block, spinal anesthesia, induced fever, or by changes in temperature or posture, all give valuable information regarding the state of the peripheral circulation. These methods give only indirect evidence regarding the major peripheral arteries. When there has been a sufficient degree of calcification of the wall, the vessel can be visualized roentgenographically but the roentgenogram gives no information regarding the flow of blood through the affected vessel.

There is need, therefore, for a method which will permit the visualization and direct study of the peripheral arterial system. Arteriography has been developed to meet this need. The ideal solution for use in arteriography should be *nontoxic*, without irritant action on the intima of the vessel, should not be painful when injected intra-arterially and should be sufficiently radio-opaque to give clear-cut visualization of the peripheral arteries after dilution by the blood stream. The solution should be excreted rapidly so as to permit repeated examination. Various radio-opaque substances have been injected intra-arterially in order to fill the vessels and permit their roentgenographic visualization. The ideal solution for use in

However, the substance may not be entirely innocuous and, because of this, it has been refused acceptance by the Council on Pharmacy and Chemistry of the American Medical Association. The report of the Council emphasizes the fact that, once fixed in the reticulo-endothelial cells of the liver and



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use in arteriography at the present time is a solution marketed under the trade name of "Thorotrast." This is a highly dispersed colloidal solution of thorium dioxide containing 25 per cent of ThO_2 . It is miscible with body fluids in all proportions without being flocculated or otherwise affected. When



Fig. 246.—Arteriosclerosis and diabetes with gangrene of the foot. Arteriogram reveals marked arteriosclerotic changes in the wall of the femoral artery with occlusion in the middle of the thigh. There is an extensive collateral circulation in the thigh. The popliteal and its branches are not involved.

injected intravenously, the thorium dioxide is picked up by the cells of the reticulo-endothelial system and deposited in the liver and spleen. This led to its introduction into medicine by Radt and Oka for hepatosplenography. Since then it has been injected by many observers for this latter purpose and nearly all observers emphasize the harmlessness of such injections.

However, the substance may not be entirely innocuous and, because of this, it has been refused acceptance by the Council on Pharmacy and Chemistry of the American Medical Association. The report of the Council emphasizes the fact that, once fixed in the reticulo-endothelial cells of the liver and



Fig. 247.—Arteriosclerosis and diabetes with gangrene of the foot. Arteriogram reveals calcification and occlusion of the femoral artery through the greater part of its extent. A small portion of the popliteal artery is patent but its branches are occluded. There is an extensive collateral circulation in the thigh and in the lower leg.

spleen in particular, excretion is slow, the greater part still being present three years later. The solution of thorotrast is radioactive, the gamma ray equivalent of 100 cc. being that of 1.24×10^{-6} Gm. of radium. This represents the maximum harmless. On the other hand, the minimal amount of radio-dose of thorotrast in hepatosplenography and is assumed to be

activity which is definitely harmful to the human body is not known.

The literature regarding the toxicity of thorotrast has recently been reviewed by Allen. He reports that hundreds of intravenous injections have been given without untoward effects. Occasional reactions do occur and one death has been reported. It would seem, therefore, that a reasonable degree of caution should be entertained in the injection of large doses of thorotrast for hepatosplenography. When thorotrast is used for arteriography, the amount needed is so much smaller that the question of toxicity is of less importance.

Arteriograms have been made in the living subject of nearly all the major arteries. Injection into the carotid permits visualization of the cerebral vessels. The abdominal vessels are demonstrated by injection into the upper portion of the abdominal aorta. The pulmonary artery and its branches have been filled, in dogs, by the passage of a catheter down the jugular vein and into the right auricle. These procedures, however, all necessitate special technics and are hardly to be classed as of wide diagnostic application. Arteriography of the brachial or femoral arteries and their branches is a much simpler procedure.

TECHNIC OF INJECTION

The arteries of the lower extremity are injected via the femoral artery in the upper part of Scarpa's triangle. The skin and the arterial wall may be anesthetized with a 1 per cent solution of procaine but, except as mentioned below, anesthesia of the femoral artery is usually unnecessary. The artery is punctured under aseptic conditions with a No. 18-gauge needle attached to a syringe containing one ampule (12.5 cc.) of thorotrast diluted to a total volume of 25 cc. with physiologic saline solution. The entrance of the needle into the lumen of the artery is signalled by a spurt of arterial blood into the syringe. The solution is then injected at a rate of 3 cc. a second. The roentgenogram is taken seven or eight seconds after beginning the injection and while it is still in progress. It is an

advantage, but not essential, to have an assistant produce partial occlusion of the artery by digital pressure above the point of injection. Separate injections are usually required for each roentgenogram of the vessels of the leg. The lateral view is usually the most informative.

The procedure for visualization of the arteries of the upper extremity is essentially the same. Repeated plates may be secured with one injection by following the technic of Allen and Camp. A segment of the brachial artery at the elbow is anesthetized with a 1 per cent solution of procaine. The artery is then punctured under aseptic conditions with a No. 19-gauge needle attached to a syringe containing from 10 to 12 cc. of thorotrast. A sphygmomanometer cuff which has been placed about the upper part of the arm is quickly inflated to a point well above the systolic blood pressure, and the contents of the syringe are rapidly injected. The cuff is deflated sufficiently to allow a small amount of blood to flow through the brachial artery. The cuff is then rapidly reinflated and a roentgenogram is made. By repeating the process of allowing a small amount of blood to flow through the brachial artery by partial deflation of the cuff twice, three roentgenograms are made. The films are exposed with the hand in three different positions: With the palm downward; with the palm upward; and with the hand in the position usually used for lateral visualization of the fingers. Following the third roentgenogram, the cuff is deflated and pressure is made for five minutes over the site of the arterial puncture.

Due care must be used in the interpretation of the arteriogram. It measures the filling of the arterial tree by the contrast medium and, unless this is complete, the interpretation of the resulting picture will be in error. Faulty or irregular injection of the thorotrast or improper timing of the roentgen exposure are the most common errors in technic. Where it is possible to take several pictures, comparison is important for the changes due to disease will be constant while changes due to technical errors will vary in the different films. Spasm of the artery may occur as a result of the arterial puncture. This

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shows no sign of active circulation through the calcified area. However, the converse has also been observed.

The development of collateral circulation is evidence of arterial disease. It is most marked in those cases in which there has been complete occlusion of a major artery such as the femoral. The extent of the collateral circulation is variable, depending primarily on the size of the vessel originally affected and on the duration and completeness of the occlusion of the latter.

The full significance of many of the details observable in the arteriogram will only be determined by detailed study and correlation of the arteriographic with the clinical and pathologic findings in an individual patient. However, enough has been done to establish the value of arteriography to the physician in the study of patients with peripheral vascular disease. The method is of value to the surgeon in determining the status of the vascular system in patients with aneurysms or arteriovenous fistulae. Furthermore, in cases of actual or threatened gangrene, whether due to embolic, arteriosclerotic, or inflammatory occlusion, arteriography is of especial diagnostic and prognostic value in showing both the position of the arterial occlusion and the extent of the collateral circulation.

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may cause sufficient temporary change in the peripheral circulation to alter the arteriographic picture. Where there is other clinical evidence suggestive of a considerable degree of spasm in the arteries of an extremity, the arteriograms should be repeated after spinal or other type of anesthesia designed to produce local paralysis of the sympathetic nerves so as to secure a maximal degree of peripheral vasodilation at the time of repeating the arteriogram. This is particularly true in thrombo-angiitis obliterans in which vascular occlusion and spasm coexist.

Once satisfactory arteriograms have been secured, examination and interpretation will depend on: (1) Congenital variations in the form and structure of the arterial tree. (2) Changes in the lumen of the different vessels as shown by irregularities in caliber, changes in diameter, or the presence and extent of complete occlusion. (3) The presence or absence of collateral circulation, its location, and extent. (4) The presence and location of abnormal vascular conditions as aneurysms, arteriovenous fistulae, or emboli and the like.

The normal artery presents a smooth outline and the shadow is homogeneous in character. When arterial disease is present, the picture varies with the pathologic condition. In thrombo-angiitis obliterans the disease is evidenced by reduction in caliber and irregularity in outline of the affected vessels. This progresses until occlusion is complete. The distal vessels frequently are first involved, the disease progressing in a proximal direction. Arteriosclerosis, on the other hand, frequently becomes manifest by irregularity of the lumen of the vessel corresponding to the development of sclerotic plaques in the wall. These may occur in vessels of any size but the process frequently is most marked in the larger vessels, especially the femoral. In the leg, for example, there may be complete occlusion of the femoral artery in the mid thigh with an extensive collateral circulation while the vessels of the lower leg show only minor degrees of involvement. When there is sufficient calcification of the wall of a vessel to render it visible in the roentgenogram, that vessel frequently is occluded and

the indicator is divided into units so that the normal pulsation of the calf of the leg is 2 to 4 units, of the thigh 3 to 7 units, of the forearm 2 to 3 units, and of the arm 2 to 6 units. Absence of pulsation or a decrease to $\frac{1}{4}$ of a unit indicates lack of patency of the major vessels at that point. Thus one may be able to determine the level of probable occlusion of the major vessel. Samuels¹ has recently designed a pulsimeter which is a modification and improvement of the Pachon Boulitte oscilometer. Its advantages over the latter consist of:

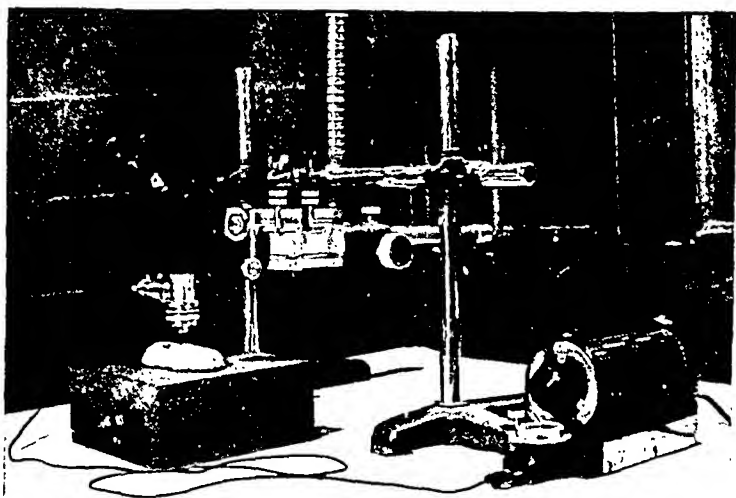


Fig. 248.—Apparatus used in observing the minute vessels of the skin. The heavy stand with mechanical adjustments permits the use over the entire surface of the body. The illumination is with the "Ultropak," using a tungsten lamp controlled by a resistance.

1. Adaptability to the physician's sphygmomanometer allowing the instrument to be made and sold at a low cost and thus making possible a wider use by the profession.

2. Elimination of a device for cutting the air connection between the aneroid and the air chamber.

3. The indicating hand returns to zero in the pulsimeter facilitating reading of the pulsation, whereas in the older instrument the needle remains in the middle of the dial.

CLINIC OF DR. DEAN A. MOFFAT

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THE MODERN APPARATUS AND TECHNIC FOR THE STUDY OF DISEASES OF THE PERIPHERAL VASCULAR SYSTEM

THE most satisfactory methods of studying peripheral vascular diseases today must include a study of the oscillometric readings of the extremities, a study of the surface temperatures of the extremities, a study of the capillaries, preferably in the fingernail bed or the nail bed of the toes, a study of the capillary pressure and the determination of the capillary permeability and fragility. Arteriography, also of great value, is discussed elsewhere in this symposium. We shall attempt to describe our own apparatus and present the technic by which such studies may be carried out under standard conditions.

Oscillometric Studies.—The oscillometer is one of the most useful instruments in the study of peripheral vascular diseases in that it tells us definitely the patency of the greater vessels. It consists of two drums, one placed within the other. The inner drum having a movable diaphragm at one end of it. These two drums are connected and there is a double connection between these two drums and a double overlapping cuff that is strapped upon the arm or leg. Upon pumping the pressure in the circuit up to the systolic blood pressure and then by means of a clamp shutting off the connection between the inner and outer drums the minute pulsations are thereby recorded on the diaphragm of the inner drum which is connected to a needle that swings back and forth over a scale. The patency of a vessel will thereby be recorded by the degree of pulsations as shown by the indicator. The scale of

capillaries, little improvement has been made until the introduction of the "Ultropak"⁷ method of illumination which consists of the principle of having the source of light striking the area to be observed at approximately the same angle of incidence that the reflected light enters the microscope, thus not producing any optical distortions of the capillaries.

Since permanent records are extremely important in making comparative studies, photography of the capillaries is of great importance. Weiss,⁸ in 1916, made a valuable contribution by recording his observations photographically. We shall, therefore, first take up the photography of the capillaries.

The first requirement in photography is to get sufficient contrast between the pink background, the subcutaneous tissue, and the red outline of the blood stream. This is best obtained by the use of a green water dye placed in a water filter. The intensity of green can be thereby varied as desired. In conjunction with the use of a filter the film for photography must be sensitive to slight color contrasts and at the same time be a fast speed film for allowing for short exposures. Through the courtesy of the DuPont Pathe Company we have obtained a superpanchromatic film which is about seven times faster than the average panchromatic film, which meets these requirements fairly satisfactorily.

The second requirement in photography is a short exposure in order to stop the motion. Exposures of one fifth to one fiftieth of a second are desirable to stop the motions which consist of the movement of the vessels themselves combined with the involuntary muscular movements of the extremity, including tremors and sometimes transmitted cardiac impulses.

We have found the most satisfactory method of immobilization to be the placement of the finger in a molded trough of plasticine, thereby steadying the finger without exerting enough pressure about the finger to hinder in any way the flow of blood. The arm should be supported in a wooden trough lined with soft padding and the hand or part to be studied should be placed about the level of the heart. With the patient comfortably arranged the entire nail fold area is

This instrument will be obtainable in a few months.

Surface Temperature Studies.—Many methods have been used to record the surface temperature such as strapping an ordinary mercury thermometer between the fingers or toes, or using the mercury thermometer with a flattened bulb and an insulating grip such as developed by Becton and Dickinson and Co. for Horton of the Mayo Clinic but none of these methods register the surface temperature quickly or accurately in that the temperature varies 3 to 5 degrees depending on the pressure exerted on the skin. A very reliable and accurate method, however, is now being used based on the thermocouple. Variations in the temperature of the couple causes varying amounts of electric current to be set up in direct ratio with the amount of variation in temperature. These slight currents are matched against known currents with a potentiometer. Many of these types of instruments are obtainable at the present time. We are using the types developed by Leeds and Northrup. The instrument used for taking individual temperature readings is adjusted by hand and the scale indicates the temperature directly in Fahrenheit and Centigrade standards. If continuous temperature is desired we use the automatic recording instrument called the "Micromax" made by Leeds and Northrup which works entirely automatically and makes a permanent record of the temperature of the skin to which the thermocouple is attached. The thermocouple has been made up in many forms so that temperatures of any part of the skin, subcutaneous tissues, intramuscular, intra-arterial or intravenous temperatures may be made.²

Tests measuring the rise in surface temperature following the use of typhoid vaccine (and other drugs), nerve blocks, spinal anesthesia, etc., are of great importance as discussed elsewhere in this symposium.

Capillary Studies.—The workers Von Kries,³ in 1875, Roy and Brown,⁴ 1878, Heuter,⁵ 1879, and Lombard,⁶ 1911, have all added contributions toward the visibility and studies of the capillaries. Since 1911, when Lombard made use of artificial lighting and higher magnification for viewing the

being taken one can observe the field and focus the microscope up until the second the picture is taken. This is accomplished by means of a focusing tube and a prism that is attached to the ocular of the microscope and the prism is swung out of the pathway of the light entering the camera the instant the picture is taken.

One of the greatest aids to visibility and clearness of pictures is proper preparation of the area to be observed. This is best done by scrubbing the area firmly with a brush, soap and water for about three to five minutes, then thoroughly drying the part. Let the area rest for about fifteen minutes before applying the oil for observation to allow the results of the irritation to subside so the capillaries will be in their normal state. Other methods used such as blistering with cantharides, heat, or removal of the superficial tissue with a razor blade will produce an area for better visibility but the vessels seen are probably not then viewed in their normal state. An oil such as mineral oil, cedar oil or castor oil (we use heavy odorless castor oil) is applied to the skin to diminish the refraction of light due to the unevenness of the skin, as suggested by Unna,¹¹ in 1891. A small cover glass may be placed over the oil as suggested by Schur¹² to keep the oil from running off the field. If the patient's hand is sweating so the perspiration mixes with the oil it causes a blurring of the field and can only be overcome by reducing the temperature of the room as the administration of drugs to reduce perspiration creates an abnormal condition.

For viewing capillaries on other parts of the body besides the fingernail fold bed and on the toes, an apparatus constructed by E. Leitz and Co. has been found to be very useful. It consists of two heavy upright stands connected by a central bar from which is sturdily supported a microscope utilizing the "Ultropak" lighting system that can be moved freely over the observed areas by a ratchet and pinion system. We use the incandescent lamp form of lighting in the instrument thus obviating the constant alignment of light rays from an arc lamp with each change of position.

best studied by moving the microscope across the field with ratchet and pinion system instead of moving the stage as is the usual procedure.⁷

The third requirement in photography is to obtain sufficient cool light applied at the correct angle of incidence and the utilization of as much of the light as possible. We have used a small bulb with a very concentrated tungsten filament filtering the rays through a green-colored heat-absorbing glass and condensing the rays with a lens system. This provides sufficient cool light for visualization but not satisfactory for short exposure photography.

An automatically fed pencil carbon arc supplies an abundance of light for photographic purposes when the rays are focused through a lens system then passed through a water-green filter so they illuminate an area of about two square centimeters on the condensing lens of the "Ultropak" system. If the water filter is thick enough a thermocouple temperature reading after fifteen minutes of continuous observation shows less than 1° C. rise in temperature of the area studied. Weiss,⁸ in 1916, used a similar method. Sheard,⁹ in 1924, and Sheard and Brown,¹⁰ in 1925, were able to increase the brilliancy of the light momentarily and use exposures of one one-hundredth of a second. But we have found with the above filter that the extreme degree of light destroys some of the contrast of the pictures.

The camera used by us is the "Leica" (E. Leitz and Co.) which uses a 35 mm. film thus allowing the use of a much smaller amount of light because of the small area of the film that has to be exposed. Also inasmuch as the camera is very small and light, it can easily be placed on the top of the "Ultropak" type of microscope (developed originally for metallurgy and adapted for capillary studies and other microscopical work by E. Leitz and Co.), thus allowing the operator to quickly assemble the apparatus and take the picture. The small negative can easily be enlarged when printing, to a 4-by 5-inch picture by means of an enlarger made especially for 35 mm. film by E. Leitz and Co. At the time the picture is

is then placed over the glass slide and focused on the capillaries. As the flow in the vessels starts or stops the pressure can be read in millimeters of mercury. The observations must be continued for a few minutes before the actual reading is taken for the blood may stop normally without any pressure being exerted on the finger. The point at which the blood flow starts, on releasing the pressure, has been considered the preferred one to be recorded. Strax and Degraff¹⁶ have recently modified the Danzer and Hooker method using a weight balance against a spring, in place of the rubber bulb for exerting the pressure and measuring it at the same time. This is a simpler method but it has not been sufficiently tried to state its value at the present time. A more accurate but likewise much more tedious and difficult method is that described by Landis,¹⁷ where a finely drawn quartz pipet is inserted into the capillary loop at various points and thereby measuring on a mercury manometer the direct pressure at any point of the capillary loop. This procedure is too difficult and time consuming to be of use in practical routine work.

Capillary Permeability and Fragility.—Another important problem of the studies of the capillaries especially in purpuric diseases is the determination of the fragility and permeability. The capillary permeability was first determined by Gänsslen¹⁸ by the well-known blister method as now described in most physiology textbooks. This method is not satisfactory. Other workers^{19, 20} have added to this method but at the present time no satisfactory method is available for determining the permeability of the capillaries. Cutter and Marquard²¹ have shown that by producing a sufficient negative pressure on a capillary bed the vessels will rupture and the blood will appear around them. From this test many interesting problems have arisen for further studies.

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Very recently polarized light has been used in conjunction with the "Ultropak" system thus giving better penetration of the light into the skin. The results of the improvement of this instrument will be reported later.

Crawford and Rosenberger¹³ in their article "Cinematographic Observations of the Human Capillaries," described in detail the method. We have not used cinematograph methods in the study of the capillaries as the cost of the equipment and making the records makes it prohibitive to examine many cases. It is also not discussed here as it requires technical knowledge beyond that of the average investigator. However, such studies give valuable information regarding changes in the blood flow and capillary appearance.

Blood Flow in the Capillaries.—Due to the fact that the rate of flow of blood in various capillaries in the field observed differs greatly, it is of little value to observe, but the "two-minute flow test"⁷ helps greatly in comparative studies in determining roughly the flow of blood in the capillaries. This is done by continually observing a capillary loop in which the blood is present at all times, for a period of two minutes and noting the number of seconds during the two minutes that the blood is not flowing. Under average normal conditions in an average individual the blood will cease to flow for a total of from ten to twenty seconds of the two minutes (120 seconds).

Capillary Pressure.—The simple method of estimating the capillary pressure first done by Von Kries,³ was to apply a glass slide to the skin and noting the amount of pressure required to produce pallor. This method was later proved to be inaccurate by Danzer and Hooker,¹⁴ and Kylin¹⁵ who showed that the blood continued to flow in the capillaries even when pallor was present. The most useful method of determining capillary pressure today is that devised by Danzer and Hooker which consists of a mercury manometer connected to a cell, the upper side of the cell is glass while the lower side of the cell is a transparent membrane. The finger is placed in a trough beneath the transparent membrane and a slight pressure exerted in the cell by means of a rubber bulb. The microscope



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THE group of clinics here presented were given at the weekly staff clinic by members of the medical department.

Arthur R. Elliott: EPILEPSIA TARDA—CONVULSIVE CEREBRAL CRISES IN HIGH BLOOD PRESSURE AND ARTERIOSCLEROSIS.

George W. Hall: NARCOLEPSY; PERIODIC FAMILY PARALYSIS; CROSSED PARALYSIS.

LeRoy H. Sloan: UNCINATE EPILEPSY.

Frank Brawley: TOXIC EFFECTS OF HAIR DYE ON EYES AND SKIN.

Geza de Takats and G. K. Fenn: THE EFFECT OF SURGICAL PROCEDURES ON THE SUGAR TOLERANCE OF DIABETIC PATIENTS. PRESENTATION OF FOUR CASES.

Harold K. Gibson: MICROCYTIC HYPOCHROMIC ANEMIA WITH PREGNANCY.

Edwin F. Hirsch: CRYPTIC BRONCHIOGENIC CARCINOMA OF THE LUNG.

Harold I. Meyer: PAGET'S DISEASE (OSTEITIS DEFORMANS).

Edward L. Jenkinson and J. M. Foley: AN INTERESTING STUDY OF BONE LESIONS WHICH PROVED TO BE MYELOMATA.

Harry Culver and William J. Baker: UNILATERAL HYDRO-URETERONEPHROSIS WITHOUT EVIDENCE OF OBSTRUCTION.

Fred E. Ball: ACUTE DIFFUSE SPONDYLITIS.

Thomas J. Coogan: ANALYSIS OF AN UNUSUAL CASE OF COUPLED VENTRICULAR BEATS.

an hour later. In the examining room he appeared to be perfectly oriented but apprehensive and confused as to what had happened. His pulse was 100 and regular, his respirations 24, and temperature normal, his blood pressure 220/130. His deep reflexes were a little slow and his pupils moderately dilated and somewhat sluggish. He complained merely of his feet being cold.

He was allowed to rest quietly in bed for two or three hours and was later carefully examined. He was able at that time to give a clear account of the preceding forty-eight hours, except for complete deletion of the period of the convulsion and an hour thereafter. His blood pressure was 230/130, pulse 112 and regular. On account of his obesity it was impossible to accurately outline the heart diameters but there were no murmurs. Gallop rhythm (third heart sound) was present. His deep reflexes were all present, rather slow and somewhat sluggish. His pupils reacted normally to light and in accommodation. There was no oculomotor disturbance and no anomalies of general motor function. The Babinski toe reflex could not be elicited. Ophthalmoscopical examination showed normal disks free from edema, a good deal of venous engorgement, and a lot of arterial fibrosis with some indications of vascular degeneration in the deep retinal tissues. He had some albumin in the urine and a few hyaline and granular casts. His blood count was red cells 4,260,000, hemoglobin 80 per cent, and leukocytes 18,500.

The physical examination which was made by myself was completed at 5:30 P. M., and we left him resting comfortably and making no complaint. The only medication administered was sodium bromide, 20 grains, at 3 P. M. About fifteen minutes after leaving the patient we were hurriedly summoned to return to his room, and found him in a strong generalized convulsion, with marked stridor and deeply cyanosed. His pulse was very full and rapid. The elbow vein was opened and 750 cc. of blood withdrawn. We had great difficulty in doing this on account of his violent convulsions. It required the united strength of two interns, two nurses and myself to

CLINIC OF DR. ARTHUR R. ELLIOTT

ST. LUKE'S HOSPITAL

EPILEPSIA TARDA—CONVULSIVE CEREBRAL CRISES IN HIGH BLOOD PRESSURE AND ARTERIOSCLEROSIS

THE recent experiences of this private patient, who has kindly consented to appear so that we may discuss his case, seem to me to be well worth consideration. They represent a dramatic episode occurring in the course of a common clinical disorder—arterial hypertension. The patient himself had no reason to suspect the imminence of such a happening and as the story is told you will see how equally unprepared we might have been had we examined him immediately before the crisis occurred.

He is forty-five years of age, 5 feet, 7 inches tall, and weighs 235 pounds. He asserts positively that he has always enjoyed robust health, has worked hard at his occupation which is that of a nurseryman and florist, and for fifteen years has not had a physical examination made, nor has he ever had his blood pressure taken. In company with his wife he motored from his home in Ohio to Chicago to visit the Century of Progress exhibition, arriving after a leisurely and comfortable trip, on October 3. He slept well that night and breakfasted as usual the following morning. At about 11 A. M. proceeding from his hotel on the south side of the city, he boarded a suburban train to visit the Fair. He chatted with his wife who sat next to him until the Fair Grounds were in sight. Without any complaint or warning outcry he suddenly lost consciousness and went into a strong generalized convulsion, became deeply cyanosed and frothed at the mouth. The convulsion lasted several minutes and was succeeded by a deeply stuporous state. He was conveyed by ambulance to the hospital, arriving about

an hour later. In the examining room he appeared to be perfectly oriented but apprehensive and confused as to what had happened. His pulse was 100 and regular, his respirations 24, and temperature normal, his blood pressure 220/130. His deep reflexes were a little slow and his pupils moderately dilated and somewhat sluggish. He complained merely of his feet being cold.

He was allowed to rest quietly in bed for two or three hours and was later carefully examined. He was able at that time to give a clear account of the preceding forty-eight hours, except for complete deletion of the period of the convulsion and an hour thereafter. His blood pressure was 230/130, pulse 112 and regular. On account of his obesity it was impossible to accurately outline the heart diameters but there were no murmurs. Gallop rhythm (third heart sound) was present. His deep reflexes were all present, rather slow and somewhat sluggish. His pupils reacted normally to light and in accommodation. There was no oculomotor disturbance and no anomalies of general motor function. The Babinski toe reflex could not be elicited. Ophthalmoscopical examination showed normal disks free from edema, a good deal of venous engorgement, and a lot of arterial fibrosis with some indications of vascular degeneration in the deep retinal tissues. He had some albumin in the urine and a few hyaline and granular casts. His blood count was red cells 4,260,000, hemoglobin 80 per cent, and leukocytes 18,500.

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hold him sufficiently still. The convulsive movements did not subside until after at least twenty minutes. Immediately after the bleeding the blood pressure was 175/130. During the convulsion the pupils were dilated and insensitive to light. There was no typical deviation.

He was seen again at 7:45 and he appeared to be oriented but somewhat confused, was sweating moderately and had vomited 300 cc. of greenish fluid. His blood pressure at this time was 150/110, pulse 120. One-sixth grain of morphine was administered hypodermically, and at midnight a tablet of amytal by mouth. He passed a rather restless night with sweating, nausea and labored breathing.

The above events occurred six days ago and the patient is leaving the hospital today to return to his home. During the interval which has elapsed since the events recounted, the patient has been fairly comfortable although somewhat weak. His gallop rhythm disappeared the day following admission and neurological examination has remained completely negative. Thirty-six hours after phlebotomy his blood pressure had returned to 200/130 and the pulse to 90. It was at all times regular and did not alternate.

From the laboratory it is reported that his blood Wassermann and Kahn tests are completely negative. The total non-protein nitrogen of the blood was 48 mg., the blood cholesterol 200 mg., and the blood sugar 120 mg. The percentage of dye excreted after kidney function test was reported to be 48 in two hours. The patient could not be persuaded to submit to a diagnostic spinal tap.

His treatment has consisted of rest, low protein diet, saline laxatives, spirits of ethyl nitrite and an occasional amytal tablet.

In review we have here a patient of stout habit and negative past history, who without warning developed severe epileptiform convulsions. Two paroxysms occurred, the second, the more severe one, within a few minutes following a medical examination during the course of which there appeared to be no warning indication of what was pending. There have been

no focal secondaries pointing to brain injury and the ocular fundus showed no indications of cerebral neoplasm or gross intracranial pressure. The laboratory reports have not revealed any kidney insufficiency and his blood Wassermann test for syphilis is negative. The one outstanding thing is the high blood pressure. We may I think fairly assume that to his entire ignorance this patient has carried a high blood pressure for a considerable period. His body type and excessive food intake certainly equip him for such developments. Moreover, the presence of thickened arteries bespeaks the strain of an elevated pressure of long duration.¹

Equally as interesting as the foregoing case is the clinical history of another patient who was under my observation in this hospital during January, 1933. This man is sixty-two, an active, temperate business man, who having become rather heavily involved with business complications during the depression, was having a good deal of anxiety. On January 26 he was in conference with his lawyer. The testimony of the lawyer is that the patient appeared to be in his normal condition when their conference began but while the conversation proceeded the patient suddenly remarked that he felt faint and dizzy, almost immediately lost consciousness and his body became rigid and convulsed. His face was suffused, he frothed at the mouth and had general rigor "just like an epileptic fit." The attack lasted several minutes and gave place to a stuporous state for an hour or more. Subsequently the patient was unable to give any clear account of what had taken place. A little later when examined at this hospital he was fully oriented and in possession of all his faculties.

Examination disclosed no evidence of sensory or motor disturbance. All his deep reflexes were active and symmetrical. His left pupil appeared to be a trifle wider than the right, but

¹ The patient's family physician reports January 2, 1934, that his body weight is 196 pounds and that he has had no repetition of the convulsions or other critical developments. His blood pressure is usually about 180/110. The urine is negative for albumin and for other morbid elements. The heart rate varies from 72 to 88. He is attending to his affairs with little decline in his efficiency.

they reacted equally to light and in accommodation. There was no tremor or speech defect and no disorder of gait. The Babinski sign could not be elicited. Ophthalmoscopical examination under mydriatic showed clear media, normally cupped disks, and no notable vascular fibrosis or tissue degeneration. His blood pressure was 160/80. The laboratory findings were as follows: red cells, 4,350,000; hemoglobin, 85 per cent; leukocytes, 14,500. Blood nonprotein nitrogen 34.45 mg., blood sugar 0.96 mg. Blood Wassermann and Kahn tests both negative.

Careful inquiry into his past history failed to reveal any similar experience and no important illnesses except prostatitis two years before. From this he appeared to have completely recovered. His habits for alcohol and tobacco were always temperate. He remained in the hospital for forty-eight hours and then went home.

He was reexamined two days later and his blood pressure found to be 160/110. The urine contained albumin, measuring 5 per cent of moist precipitate in the centrifuge. The urinary sediment revealed neither pus nor blood cells, and but one granular cast was seen. It appeared to be likely that this patient had a nephritis which despite the absence of azotemia might be in some way causal for his convulsion. He was advised to rest for a period in a warm climate, where he might be out-of-doors in the sunshine. This he did apparently to his great advantage, returning to his business affairs after a month's absence much invigorated and without in the meantime having had a mishap of any kind. He attended his office daily. *According to his secretary he showed nothing unusual in his behavior or his work.*

About noon of March 30 while dictating a letter he hesitated and then suddenly lost consciousness. He became rigid and passed into a generalized convulsion, with puffing breaths and bubbles on his lips. I saw him just as the convulsion ended. He was at that time not oriented and did not respond to questions. His face was flushed and the temporal arteries stood out prominently. His pupils were equal, of midsize and

responded normally. He had not bit his tongue. His knee jerks were active and equal. Later he tried to answer questions but his words were jumbled and used without any meaning, mainly words having to do with his business without consecutiveness. Within an hour he was able to leave his office on foot and proceed to his home, apparently little the worse for his experience.

From that day to this there have occurred no further cerebral manifestations of any kind, the patient attending to his affairs under the compulsion of necessity, although with a more conservative personal hygiene.

A third clinical history more elaborately illustrates this interesting development. This patient is a friend of mine, a rather corpulent and plethoric man, who had retired from active participation in his business when my clinical record was started in 1921. He was at that time sixty-nine years of age. His complaints were vertigo and tinnitus without impairment of hearing. He had been examined by a competent aurist without finding any particular involvement of his ears except some impacted cerumen, the removal of which appeared to make little difference in the tinnitus which affected both ears equally. His vertigo was not severe and occurred irregularly without much connection with body posture. The other complaints were gas on his stomach and some substernal tightness, although he was not short of breath on exertion and did not rise at night to urinate. He had an excellent family longevity and seemed in general to be a well-preserved man for his years. His blood pressure was 160/100 and his heart slightly enlarged. There was some skipping of the pulse and he had a rather harsh systolic, sclerotic type of murmur over most of the heart area. His retinal arteries appeared to be moderately sclerotic, producing a fair degree of arteriovenous compression. Periodic examinations were made through a period of five years without any notable development.

On January 18, 1927, while sitting one evening after a moderate meal doing a cross-word puzzle, he suddenly lost consciousness, became cyanotic and rapidly passed into a

they reacted equally to light and in accommodation. There was no tremor or speech defect and no disorder of gait. The Babinski sign could not be elicited. Ophthalmoscopical examination under mydriatic showed clear media, normally cupped disks, and no notable vascular fibrosis or tissue degeneration. His blood pressure was 160/80. The laboratory findings were as follows: red cells, 4,350,000; hemoglobin, 85 per cent; leukocytes, 14,500. Blood nonprotein nitrogen 34.45 mg., blood sugar 0.96 mg. Blood Wassermann and Kahn tests both negative.

Careful inquiry into his past history failed to reveal any similar experience and no important illnesses except prostatitis two years before. From this he appeared to have completely recovered. His habits for alcohol and tobacco were always temperate. He remained in the hospital for forty-eight hours and then went home.

He was reexamined two days later and his blood pressure found to be 160/110. The urine contained albumin, measuring 5 per cent of moist precipitate in the centrifuge. The urinary sediment revealed neither pus nor blood cells, and but one granular cast was seen. It appeared to be likely that this patient had a nephritis which despite the absence of azotemia might be in some way causal for his convulsion. He was advised to rest for a period in a warm climate, where he might be out-of-doors in the sunshine. This he did apparently to his great advantage, returning to his business affairs after a month's absence much invigorated and without in the meantime having had a mishap of any kind. He attended his office daily. According to his secretary he showed nothing unusual in his behavior or his work.

About noon of March 30 while dictating a letter he hesitated and then suddenly lost consciousness. He became rigid and passed into a generalized convulsion, with puffing breaths and bubbles on his lips. I saw him just as the convulsion ended. He was at that time not oriented and did not respond to questions. His face was flushed and the temporal arteries stood out prominently. His pupils were equal, of midsize and

memory is deteriorating, but considering his age there appears to be doubtful merit to that statement.

His blood pressure varies from 150/90 to 180/100 and his pulse from 50 to 72, with occasional skips. The electrocardiogram shows a normal mechanism without any increase in the P. R. interval. The urine is free from albumin and sugar. For eighteen months he has been on luminal from $1\frac{1}{2}$ to 2 grains daily and this appears to stabilize somewhat his rather sensitive emotionalism, and abate the severity of his attacks.

This patient is now eighty-two years of age, enjoys activities commensurate with his time of life, retains his faculties satisfactorily, travels a good deal and attends to minor matters connected with his affairs despite the fact that during the past five years he has had at least twelve epileptiform convulsive seizures of the grand mal type and very many minor manifestations of petit mal character. One would hardly have felt warranted in giving such a prognosis at the time of the stormy advent of these attacks in 1927.

DISCUSSION

It is a curious fact regarding which anyone who looks into the matter may satisfy himself, that American medical literature appears to display a singular indifference to the importance of epilepsy as it develops during the later decades of life. Continental European periodicals and neurological reviews contain frequent and often detailed discussions on the subject, but like sources in this country, which furnish many notable contributions having to do with idiopathic epilepsy in the young, yield little information regarding *epilepsia tarda* or, as it has been called rather erroneously, *senile epilepsy*. It is just possible that the reason for this is that epilepsy of the aged constitutes more an interest falling under the attention of the internist instead of the neurologist and that the former has been derelict rather than the latter.

Under the title of "*epilepsia tarda*" Riesman and Fitz-Hugh, Jr.,¹ in 1927, reported a number of cases of generalized con-

¹ *Annals Int. Med.*, 1: 273, 1927-28.

general convulsion which lasted several minutes. Following this attack he was very drowsy and was aroused with difficulty. During the four succeeding days he had several more convulsions of like character, some of them accompanied by involuntary discharge of feces and urine. He was bled on January 20th and again on the 22nd. On February 9th he experienced a mild attack of mental confusion without loss of consciousness. For a month he had hemianopsia and for two months more or less amnesia. He gradually returned to his usual health and activities and did not experience any further difficulty until the following October 9, when he had a mild cerebral attack characterized by mental confusion and disorientation but without convulsion.

The next development occurred on February 19, 1928, and was of mild character. Ten months later, December, 1929, he experienced a severe generalized epileptiform convulsion with postconvulsive stupor but without sphincteric relaxation. Since that time his seizures have been uniformly milder but more frequent, averaging from four to ten weeks apart, and he has had no more involuntary movements. The record of seizures for the year 1933 is as follows: April 23, two attacks, one mild and one severe; April 24, one mild attack; April 27, two attacks mild in character; August 19, one severe and two mild; October 21, one mild; November 21, two attacks, one mild and one severe; November 22, one mild attack. During the past two years he has had increasing number of minor sensory disturbances which may perhaps be classed as *petit mal*. These are described by the patient as a "queer" sensation, like a numbness starting from the region of the xiphoid and traveling upward along the left border of the sternum to the tongue, chin, left side of the upper lip and over the face to the forehead. Coincidentally he has a sense of mental confusion, but the whole affair is over quickly and the patient is immediately himself again, the whole affair lasting but a half minute. I have seen him in several such attacks and were it not for a certain limpness of body the observer would hardly be aware that anything is the matter. The patient insists that his

memory is deteriorating, but considering his age there appears to be doubtful merit to that statement.

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vulsions occurring for the first time in later adult life and discussed their pathogenesis. With the exception of this article American sources for a decade or more are singularly silent regarding this problem. From this it would, I think, be erroneous to infer that the phenomenon is a rare one in this age class. I have from time to time during the past twenty years had a good many cases come to my attention and the fact that these three patients so affected are at present under observation is not a mere coincidence.

Belonging in the same class of functional disturbances is the large series of transient cerebral dysfunctions which if all were classed together, as doubtless etiologically they should be, they would make in all a considerable and important group. Osler¹ wrote most interestingly of these phenomena, although he did not describe but merely mentioned convulsions as among the cerebral manifestations of high blood pressure and arteriosclerosis. He did, however, dwell upon transient attacks of aphasia, amnesia, sensory disturbances and motor paralysis. Transient amaurosis and fleeting oculomotor phenomena are also to be included and doubtless they may be considered as resting on the same etiologic foundation; as being related in some way to transient disturbances in cerebral circulation incident to arterial degeneration and elevated blood pressure.

One feels a certain diffidence in venturing any assertive explanation as to the mechanism of the convulsive state be it in the aged or the young. About as far as we appear to have got in our comprehension of the convulsive state is that it is brought about by cerebral anemia; in other words, is due to insufficient oxygen supply to the cortical tissues. Supporting this contention stands the suggestive fact that blanching of the cortex has repeatedly been observed during exploratory craniotomies not only in animals but also in human beings, just before and at the beginning of a convulsion. It is well known that generalized convulsions may follow profuse hemorrhage from any cause, may accompany states of profound shock and during violent vasomotor shifts as when pleural accumulations are too rapidly

¹ Canadian Med. Assn. Jour., 1: 919, 1911.

withdrawn. The present view with respect to the idiopathic epileptic convulsion is that it is due to increased fluid pressure in the subarachnoid spaces over the surface of the brain confined within an unyielding skull, thereby interfering by compression with the cortical pathways for cerebrospinal fluid circulation. This is hydrostatic intracranial pressure causing tissue anoxemia. In the same manner convulsions in uremia and eclampsia may be produced. In epilepsy beginning late in life we cannot avail ourselves of this extravascular mechanism but must ascribe the cerebral anemia to some cause directly arising within the cerebral arterial circuit. Doubtless, true idiopathic epilepsy may occasionally begin beyond the age of forty, but the vast majority of cases of *epilepsia tarda* occurs in individuals having either high blood pressure, arterial degeneration or both. Vasomotor control of the cerebral vessels is now a well-established fact. Physiologically it has been shown that the cerebral vessels may constrict and dilate under an appropriate stimulus. Real obliterating angiospasm, however, has only been seen in the laboratory when the vessels are strongly and locally stimulated under nonphysiologic conditions. There is some basis for the assumption that fibrotic arteries are apt to constrict more actively under stimulus than do normal vessels. In lieu of a better explanation we may assume that the entire group of transient cerebral dysfunctions, including convulsions as observed in the aged, is the result of sudden obliterating angiospasm in the cerebral arterial circuit. In this connection Bordley and Baker's¹ observations may possess significance. These pathologists established a constant association in their autopsy material between sclerosis of the arteries of the brain stem and persistent states of hypertension. Other pathologic studies, notably those of Gull and Sutton, and of Pal have demonstrated the great frequency with which arterial changes exist in the brain in persistent vascular hypertension. Some confirmation of the vascular theory is furnished by Naunyn's experiments, for in three patients with senile epilepsy he was able with constancy to reproduce typical

¹ Bull. Johns Hopkins Hosp., 39: 229, 1926.

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A few minutes' consideration should be given to the problem of differential diagnosis. The sudden occurrence of convulsions in an individual of mature years, especially if he were known beforehand to have high blood pressure, will very naturally suggest uremia as the cause. Almost before the blood chemistry report is available our suspicions in this regard will very likely be dissipated for the patient has returned to his *status quo ante* and appears none the worse for his experience.

Central nervous syphilis, cerebral neoplasm or some intoxication, such as alcohol, or the Stokes-Adam syndrome will also come to mind. There should prove little difficulty in solving the problem except in the case of brain tumor and here we may have to wait for further developments to be sure of the diagnosis. Parker¹ states that out of 313 patients with brain tumor, 67 had convulsions and in 38 of these, fits constituted the first and in 13 patients the only symptoms present for one or more years preceding further developments. Only after a certain lapse of time can one be absolutely sure that he is not dealing with an occult cerebral neoplasm.

The etiologic balance between arteriosclerosis and hypertension is difficult to exactly define. There is much classical argument existing to prove that vascular overexcitability is a main characteristic of hypertension in contradistinction to pure arteriosclerosis and that angiospastic attacks do not occur in the absence of high blood pressure.

What direct quantitative relationship exists between the height of the blood pressure and liability to convulsions is not at all clear. One may never have an opportunity to know the exact height of the pressure just before the fit. That it is high soon after is not surprising and need not be considered significant. The convulsion may not follow excitement or effort or meals, such factors as would elevate blood pressure. As often as not it comes suddenly out of a clear sky, while the patient is at rest or about his usual interests and occupation. It seems, however, only rational to assume that vascular irritability will be greater under the stimulus of a sudden rise in blood pressure.

¹ Arch. Neur. and Psych., 23: 1031, 1930.

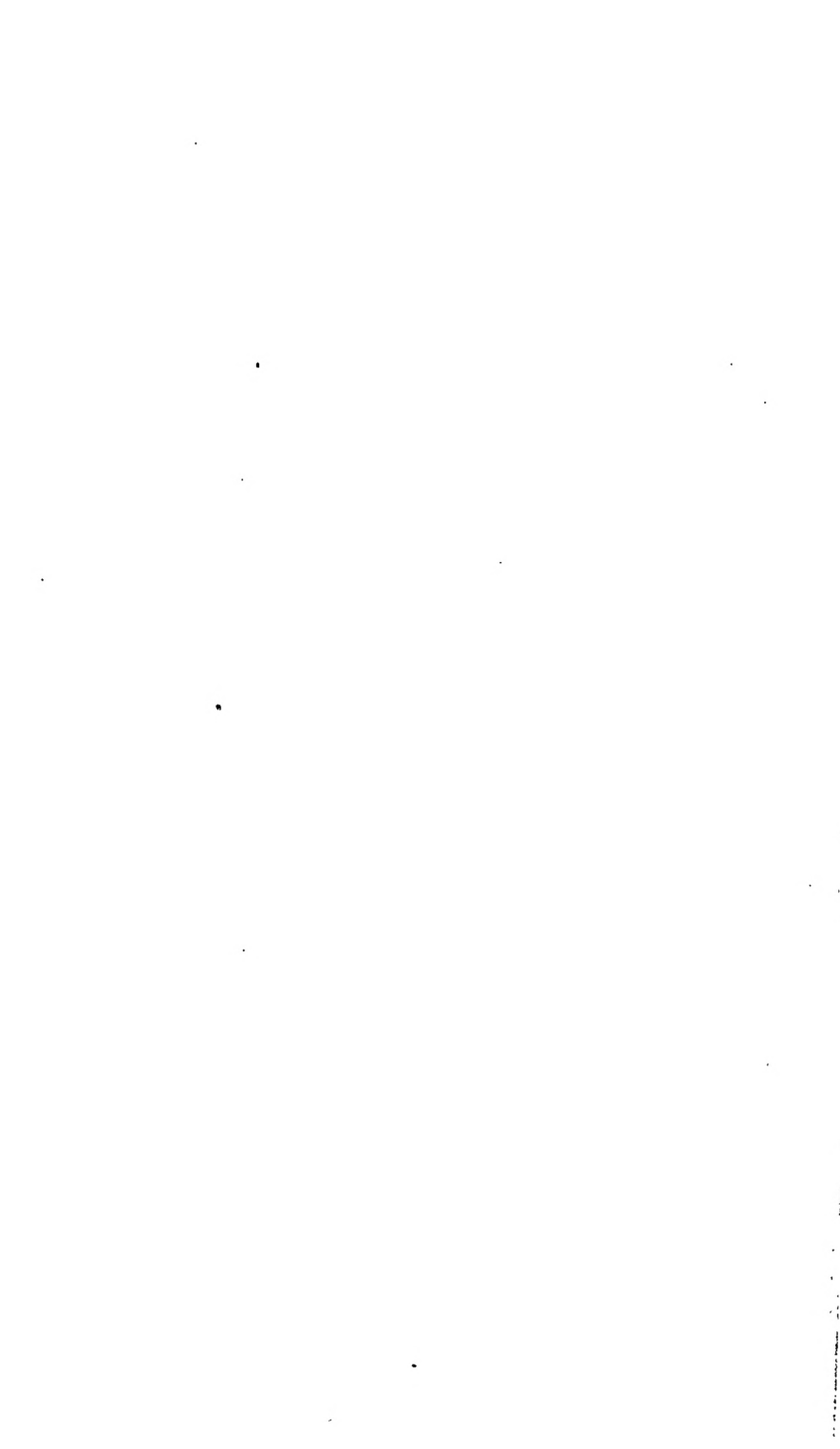
grand mal attacks by manual compression over the carotids. By the same expedient he succeeded in initiating fits in a few other nonepileptic but arteriosclerotic individuals, whereas carotid compression was ineffectual in a group of healthy adults.

Were it necessary to array evidence in support of the theory that fits may be the result of vascular spasms, we have but to turn to the succession of events in Raynaud's syndrome and in so-called "Buerger's disease." Moreover, we have suggestive developments in the coronary and cerebral circulations in heavy cigaret smokers. Unlike convulsions arising from traumata or secondary to gross anatomical lesions within the cranium, the nature of the seizures in *epilepsia tarda* is precisely similar to those of idiopathic epilepsy occurring in early life. The sequence of events is almost invariably the same, aura, more or less distinct tonic and clonic motor spasms, tongue biting, sphincteric insufficiency, and postconvulsive stupor. The attacks may be either major (grand mal) or minor (petit mal), although there appears to be a greater tendency toward severe convulsions as the type in epilepsy of the aged.

The effect upon the mental functions is not so pronounced as might be supposed, although the patients' age and underlying vascular degeneration predisposes them, especially under the recurring strain of convulsions, to progressive mental deterioration. Noticeable impairment of memory is the most frequent observable effect. Cerebral thrombosis, or hemorrhage during an attack may cause paralysis. Angina or cardiac collapse are not infrequent. The higher the average blood pressure the greater appears to be the danger of such complications. Despite these and other risks, the cerebral arteriosclerotic epileptic may live for many years. Anglade¹ reported a patient living eight years after the first convulsion, Riesman and Fitz-Hugh one surviving in nine years, and Janeway,² one four years. The third case discussed today has survived six years since his initial seizure and considering his advanced years is in tolerably good health and mental efficiency.

¹ Jour. de Med. de Bourdeaux, 90: 356, 1919.

² Arch. Int. Med., 12: 755, 1914.



Consequently it is good judgment to limit somewhat the indulgences of these patients and insist upon a conservative personal hygiene.

For therapy we have no other lead to follow than the measures employed in idiopathic epilepsy, namely, salt and fluid restriction, bromides and luminal, with perhaps one of the xanthine derivatives such as theobromine or theophylline.

accommodation. There was no cranial nerve paralysis. There was no tremor or weakness of the extremities. Deep tendon reflexes were all lively and equal. There was no Hoffmann nor Babinski sign on either side; no ataxia of station or gait; no objective sensory disturbance.

The patient married about four and one-half months ago. She has had considerable difficulty in arriving at certain adjustments with her husband and for that reason she thinks that the attacks became more frequent for a time. The question came to our minds as to whether or not we were dealing with a possible hysteria, as she states that she had an attack of aphonia on one occasion and noticed considerable palpitation of the heart.

Taking into consideration the two types of complaints so to speak, in this case, namely the attacks of somnolence coming on suddenly without a previous sensation of being sleepy alternating with definite cataplectic attacks when she would fall down and become very weak and unable to rise for a few minutes following this emotional reaction, caused us to come to the conclusion that she was suffering from a definite narcolepsy.

In order to eliminate the possibility of these being hysterical attacks, however, we applied a therapeutic test consisting of the administration of $\frac{3}{8}$ grain of ephedrine sulphate three times a day. Immediately following the administration of this drug the patient had no more attacks as have just been described. She continued with this medicine for a few weeks and then she came in with the statement that she had finished with the medicine and after a period of three weeks without medicine she had a return of these attacks of somnolence with the cataplectic attacks. Her last visit was on December 4, 1933, when she reported that she had no attacks of any description since her previous visit as she had continued the medicine daily.

The next patient, W. K., aged twenty-four years, a salesman by occupation, came to the clinic with the statement that he had irresistible attacks of somnolence which had begun

CLINIC OF DR. GEORGE W. HALL

ST. LUKE'S HOSPITAL

NARCOLEPSY

I HAVE purposely chosen a definite group of cases to present to you this morning because of the unusual interest manifested in the symptoms given by these patients as well as the etiologic factor associated in one of the cases.

The first case I wish to present is a young lady, twenty-six years of age, a telephone operator by occupation. She was first examined by me on May 1, 1933. Her family history was negative as far as present complaints were concerned. Her past history showed that she had an attack of influenza accompanied by dizziness in December, 1932. She came in with the complaint of having had definite attacks of weakness, as she called them. She stated that for the past five years she had had attacks of somnolence. She would return from her work in the afternoon and would suddenly feel a sense of drowsiness coming over her. She would lie down and perhaps would sleep for an hour or two, and possibly to dinner time. In February, 1933, while at her switchboard her eyes would close suddenly and her head would drop with these attacks of somnolence. She was unable to resist these attacks, although she would get up and occasionally wash her face in cold water and seek other diversion. In April, 1933, she gave up her work because of these attacks of drowsiness, as she called them. One week later after partaking of a heavy evening meal she got up from the table and suddenly became very weak and fell to the floor. She has had similar attacks as often as three times in one day. These attacks always followed some emotional disturbance, such as laughing at a joke or becoming surprised or after some emotion of joy.

Neurological examination showed that the fundi were normal and that the pupils reacted normally to light and in

Physical examination revealed no evidence of organic disease involving the central nervous system. His pupils reacted normally to light and in accommodation. There was no cranial nerve paralysis. All the deep reflexes in the upper and lower extremities were present and normal. The abdominal reflexes were decreased. Blood pressure was 108/50 and pulse 60 per minute. On testing him out for sensory disturbance we found that his reactions to pinprick were normal over every part of the body. So also was tactile sense, vibration and joint sense normal.

At our request, Dr. Eric Oldberg made an encephalogram in order to exclude any possibility of organic change in the brain and the report was returned that nothing abnormal was found. Consequently this patient presents two definite phases, namely attacks of drowsiness, alternating with definite attacks of weakness which we speak of as cataplectic attacks, which are characteristic of narcolepsy. This patient has been placed on ephedrine, $\frac{3}{8}$ grain, three times a day. Since the beginning of this treatment he has had no attacks of somnolence.

I might call your attention to an article by H. A. Cave appearing in the Archives of Neurology and Psychiatry, July, 1931, in which he gives a classification of narcolepsy. These two cases which I present today might fall into the class with a history of influenzal attacks, as being probably encephalitic in origin.

This disease was first described by Westphal in 1877 and later by Jelineau in 1880. In 1928 Kinnear Wilson of London made a very exhaustive study of the literature and reported several cases of narcolepsy.

In considering the diagnosis of narcolepsy from the standpoint of attacks of drowsiness as well as cataplectic attacks, other diseases must be considered, especially epilepsy, including so-called "petit mal" attacks, and one of these cases presents that difficulty.

In differentiating narcolepsy from epilepsy one must be able to determine whether or not the patient actually loses consciousness during one of these so-called "weak spells" or

about a year and a half previous to his first visit here. The family history was negative. On going into his personal history we found that he had what was diagnosed as influenza ten years ago. He was confined to bed for about two months, and during that period was unconscious for two days. He gave no history of havng had any other illness. These attacks of sleep occurred on an average of about once a week in the beginning but gradually increased in frequency to as many as one to three attacks per day. They would come on without warning and without any previous feeling of drowsiness. On some occasions while talking with a client he would have these attacks of somnolence. On other occasions while eating he would go to sleep, and on still other occasions he would have a similar attack while driving his automobile. About six months ago he had such an attack and drove his automobile through a redlight signal, striking another car and damaging it to the extent of \$100.00 worth. Since then while driving he has been able to park his car before extreme somnolence takes place, as he now understands the uselessness of resisting these attacks. He states that he has scary dreams occasionally during an attack, and feels as though he is being chased by some animal. These paroxysmal attacks of sleep last from a few seconds to a half hour, when he awakens feeling quite refreshed, although very much discouraged because of its interference with his business. If he attempts to resist these attacks he becomes very nervous and feels as though he were on marked mental or nervous tension. He also gives a history of having fallen to the floor from a chair and having to be helped to his feet because he was too weak to get up without assistance.

On being interrogated as to whether emotion had any relation to these spells he replied, "yes, when I laugh or when somebody cracks a joke I become very weak and shaky, and sometimes I fall to the floor; although I am perfectly conscious during the attack I seem to be absolutely helpless. I feel as though I want to laugh and cannot laugh." He states that during the past five months he has gained about 10 pounds in weight. He drinks much more water than he formerly did.



cataplectic attacks. For that reason I have emphasized the fact that these patients have stated that at no time were they unconscious although too weak to express themselves.

Referring again to Cave's article, his conclusions are that in order to make a diagnosis of narcolepsy the two phases must be taken into consideration. All gradations between sleeping attacks with cataplexy to cataplexy without sleeping attacks may occur. The sudden onset, brevity of the attack and rapidity of recovery of the two types of attack are more or less characteristic. He further states that narcolepsy may occur as a sequel of epidemic encephalitis, and mentions also the possible relation of these attacks of sleep to organic lesions of the floor of the third ventricle or the aqueduct of Sylvius. We might add that brain tumor in that vicinity might produce very definite attacks of somnolence. To our knowledge there has never been an autopsy held on a narcoleptic. Consequently, we are not in any position to draw conclusions as to the possible pathology of the disease.

The treatment is purely symptomatic and not a specific as far as the cure of the disease is concerned.

normal. The abdominal reflexes are somewhat decreased. The knee jerks and Achilles jerks are all present and normal. There is no ataxia of either the upper or lower extremities. The vibration, touch, pain, position and temperature sense are all normal. There is no spasticity in either the upper or lower extremities and the Babinski is absent on both sides.

Less than thirty-six hours ago this patient was examined and it was found that he could not lift his head from the pillow when lying on his back. There was no contraction of the sternocleidomastoid muscles, while the chest contracted and expanded normally, and the excursions of the diaphragm were normal. Relative to the upper extremities, he could not move either arm and the grip was nil in both hands. The biceps and triceps jerks could not be obtained. The abdominal reflexes were present, as were the cremasterics. He could not move either leg. The knee jerks and Achilles jerks could not be obtained on either side. There was no Babinski on either side, and no bladder or rectal disturbances, nor were there any sensory disturbances. We also tried out the electrical reactions and found that the muscles of the arms and legs did not respond to faradism, and gave a very slight response to galvanism. We have done various skin tests on him to note any reactions to the different foods which included a large list of foods. All such tests proved to be negative. The urine is normal. The blood chemistry is normal, except that the sugar content of the blood shows 137 mm. per 100 cm. of blood. We have not as yet been able to test out his urine for the presence or absence of creatin.

The diagnosis of periodic family paralysis has been made in this case, which as you know, is a comparatively rare disease. The question of hysteria of course must be excluded. We are unable to elicit any mental conflicts. Another important diagnostic point in excluding hysteria is that during the attacks of paralysis the patient's deep reflexes are all absent, and the electrical responses showed definite diminution, rather than an increased response, as one would expect in hysteria. We are unable as yet to recommend any treatment which can in any way influence these attacks.

PERIODIC FAMILY PARALYSIS

THE third patient which I wish to present for your consideration is a young man, J. K., twenty-one years of age. He states that he was perfectly well until about nine years ago when he had his first attack of paralysis. This came on suddenly without warning. His arms and legs were completely paralyzed, although he had no difficulty with his speech. His breathing was normal and the excursions of the diaphragm were normal. There was no cranial nerve paralysis. He could chew and swallow in a perfectly normal way. He had full control over his bladder. There were no subjective sensory disturbances over any part of the body. This attack lasted for about twelve hours when it gradually disappeared, and he was able to walk about and do his work as usual. These attacks recurred every two or three weeks in the beginning, but as time has elapsed they have become more frequent so that now he has attacks of paralysis as often as once and perhaps twice a week. No attack of paralysis has lasted more than two days. The average length of time has been from twelve to fourteen hours. Occasionally he has the feeling, as he states, that a spell is coming on, but usually they come on without previous warning. Between the attacks he can do ordinary gymnastic exercise, run, and do the usual amount of work. His family history is negative as far as any relationship to his present illness is concerned. His father and mother are living and well, and he has two sisters living and in good health. None of them are subject to attacks similar to those of which he complains. He states, however, that one uncle had similar attacks for a number of years, but in recent years has not been troubled. His habits are good. He does not use alcoholic liquors in any form.

Neurological examination shows that the vision is normal. The optic nerve disks are normal and all the ocular movements are normal. There is no strabismus and no nystagmus present. The tongue protrudes in the median line. The grip is good in both hands. The biceps and triceps jerks are present and

régular in outline. The optic nerve disks were normal. On testing out his tendon reflexes we found that the right biceps was more lively than the left. The abdominal reflexes were absent on the right and present on the left. The right patellar knee jerk was much more exaggerated than the left. There was a positive Babinski on the right side and negative on the left. There was a positive ankle clonus of the right foot and negative on the left side. We might add that he could move his eyes in any direction on following the finger. There was no diplopia. On testing out for sensory disturbances we found that he could feel a pinprick as well over the entire right side as over the left side. There was no disturbance of temperature or tactile sense on either side.

My reason for presenting this case is that he shows a definite crossed paralysis, namely a peripheral paralysis of the left side of the face with a paralysis of the right arm and leg, but with no paralysis of the right side of the face. The paralysis came on gradually without loss of consciousness, and even though this patient has a high systolic pressure we have made a diagnosis of thrombosis rather than hemorrhage. It is our opinion that he had an occlusion of the left branch of the basilar artery which supplies the pons on the left side.

This picture resembles somewhat the so-called "Millard-Gubler syndrome." It is a modified type of that syndrome because of the absence of sensory disturbances over the right arm and leg and because of the absence of involvement of the sixth nerve on the left side. A typical Millard-Gubler syndrome, as you will perhaps recall, produces a paralysis of the left side of the face, either involving the nucleus of the left facial nerve or the intrapontine fibers of that nerve, and because of its being in close relation to the nucleus of the sixth nerve, the sixth nerve is for that reason usually involved. The face fibers coming from the left cortex cross over higher up and consequently the right face is not involved, whereas the arm and leg fibers are involved in this lesion, producing a paralysis as above stated. In addition to that, one usually expects sensory disturbance over the right side of the body which is not

CROSSED PARALYSIS

THE fourth case which I wish to present is that of W. G., a male, aged forty-nine years, married and a barber by occupation. He entered the hospital on January 4, 1934, as a patient of Dr. William R. Cubbins who very kindly gave me the privilege of examining the patient. His complaint is paralysis of the left side of his face accompanied by paralysis of the right arm and right leg. The patient states that he has had high blood pressure for the past two or three years, but that he was in average health and able to carry on his occupation until November 8, 1933, when he noticed that his face was pulled over to the right and he had some difficulty in talking and in chewing. Liquid foods would escape from the left side of his mouth. This attack was not accompanied by any loss of consciousness or any other subjective symptoms. Examination at that time showed that he was unable to close the left eye, he could not wrinkle the left half of the frontalis muscle. He also had complete paralysis of the lower facial group of muscles on the left side. Nothing additional was noted until the night of December 26, 1933, when about three o'clock in the morning he awoke with a peculiar dizzy feeling in his head. He attempted to go to the bathroom, but walked with much difficulty because of weakness of the right arm and right leg. He was able to return to his room, however, without assistance although he noticed this definite weakness of the right arm and right leg. His past history is negative. He denies any venereal disease. He underwent a cholecystectomy and an operation for peptic ulcer nine years ago. With the exception of the high blood pressure, which he has already mentioned, there have been no cardiac complaints.

Neurological examination when he first came to the hospital showed a complete peripheral paralysis of the left side of the face, with complete paralysis of the right arm and leg. The pupils reacted to light and in accommodation and were



present in this case, and it is for these reasons that we classify this as a modified type of Millard-Gubler syndrome.

Since his rest in the hospital and under the administration of potassium iodide in gradually increasing doses, the patient has made considerable improvement, so that at the present time, as you can see, he is able to move his right arm and right leg very perceptibly. He is also able to close the left eye about 50 per cent better than when he first came to the hospital. I might add that the Wassermann test on the blood is entirely negative. His hemoglobin record shows 75 per cent; red blood count 4,220,000, leukocyte count, 7900. There is about 30 mg. of albumin per 100 cc. of urine present.

Our belief is that this patient will make still further progress unless another attack occurs. He should have fairly good use of both the right arm and right leg. The left face is still showing improvement and we believe it will make a very good recovery.

She noticed a *bad odor* which seemed to be in the left nostril and which she describes in the rather vague terms of "like chloroform" or "like gas," at any rate strange and unusual. She reached for her false teeth, tried to take them out, went into a major convulsion, became stiff as a board. Not for an hour was she fully recovered and able to talk to her excited neighbors. Since this time she has had several seizures. We shall attempt only to describe the composite picture.

The typical attack is *always* characterized by this *bad odor*, it is *always* referred to the general region of the left nostril, and is *almost* always followed by a still more important manifestation, namely the appearance in the zone of her consciousness of the *name of a girl friend in old England* and the appearance at times of the *features* of this girl friend. Apparently the patient actually *hears* the name of this friend. I am unable to determine if the appearance comes into any definite visual field. Following the occurrence of the bad odor, and the appearance of the friend of her youth the patient has a major generalized convulsion from which she arises exhausted and with a frontal headache at times made even more tragic by the loss of memory for a period of three or four hours. In the postconvulsive period she has noted a soreness of the right arm and the right side of her chest and her right shoulder. Some of her attacks are not completed by a convulsion. She feels very *queerly*, feels as if she were *passing away*, but does not quite lose consciousness. She states that on one or two occasions she has "fought them off by trying to think hard" or by forcing herself to get up. (It is not uncommon for patients to insist that they are able to partially control the onset of a major convulsion particularly originating in the temporal lobe.)

Her examination is almost negative. Her urine, blood Wassermann, blood Kahn, blood count, spinal fluid, etc., are all within the range of normal. Her blood pressure is normal. Neurological examination shows the left pupil larger than the right, the tongue deviates a bit to the right, there is a positive Hoffmann reflex on the right side, and there is an equivocal plantar on the right side. Her fundi and disks are normal.

CLINIC OF DR. LEROY HENDRICK SLOAN

ST. LUKE'S HOSPITAL

UNCINATE EPILEPSY

IN the preceding pages Dr. Hall has called attention to an unusual and dramatic variant of the ordinary picture of epilepsy. I wish to direct your interest to a specialized type of the same disease which is probably somewhat more common but none the less dramatic. In a certain sense this type is focal in nature in that it originates in a disturbance of a specialized area of the brain, spreads frequently to contiguous structures and then marches on to a general convulsion. It has been referred to by some as psychic hallucinatory epilepsy. In reality it is an *epilepsy* which starts in a *focal* area of the much larger and superimposed silent temporal lobe. For years the temporal lobe has been called the silent area and especially the right temporal lobe. In spite of much study this lobe still remains comparatively silent yielding little by little to the study of Cushing on the geniculocalcarine radiations, of Walker on the results of careful perimeter studies of the smaller defects of the visual fields, and finally to the results of ventriculographic study.

Our patient is an English lady of forty-one years of age. She comes into the dispensary complaining of "fits." This is the term which English laymen and physicians alike apply to the disease epilepsy. She states that her fits began one year ago, at the age of forty years. At first her attacks were only present at night and occurred every two or three weeks. They were observed by the husband of the patient who noted only the convulsive features. However, shortly thereafter the attacks began to come in the day time. The first attack of which the patient is entirely cognizant came on at about 3:30 p. m.

appear to be passing away but all of the time remaining conscious. She could only describe the whole episode as "feeling queer as if she were going to pass away." With the appearance of paresis of the left arm and face the localization of a deep-seated temporal lobe tumor became apparent and at operation a large infiltrating tumor was found in such location. Usually the patient describes the odor as distinctly bad, much less often as pleasant. In other patients actual bells are heard, crude sounds appreciated and rather a systematized march of

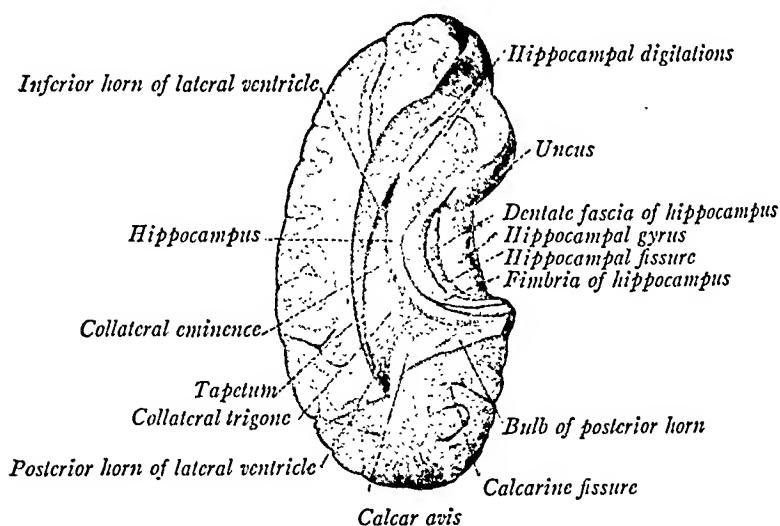


Fig. 250.—Part of temporal lobe of human brain showing inferior horn of lateral ventricle and the hippocampus. Dorsal view. (Sobotta-McMurrich.)

colors. Recently a patient in my ward at Cook County Hospital described his attacks as always preceded by a fading away of objects. Persons became smaller and smaller appearing to travel toward the horizon only suddenly to disappear with the onset of a major convulsion (micropsia). Now if we examine the brain of sheep we find (Fig. 249) the large expanse which the olfactory area takes in. We are struck by the extent of this important area in the animal as contrasted with the smaller area, the more compact make-up and the apparent seclusion in man. In the fish for example there is a primordial olfactory

Where is the focal point of origin and what portion of the brain is involved in the picture presented? Now we have most of the elements for so-called "uncinate epilepsy," or temporal lobe epilepsy as it more properly might be termed. It is due to irritation in or close to the uncus or tip of the temporal lobe, is associated with a spread to other portions of the temporal

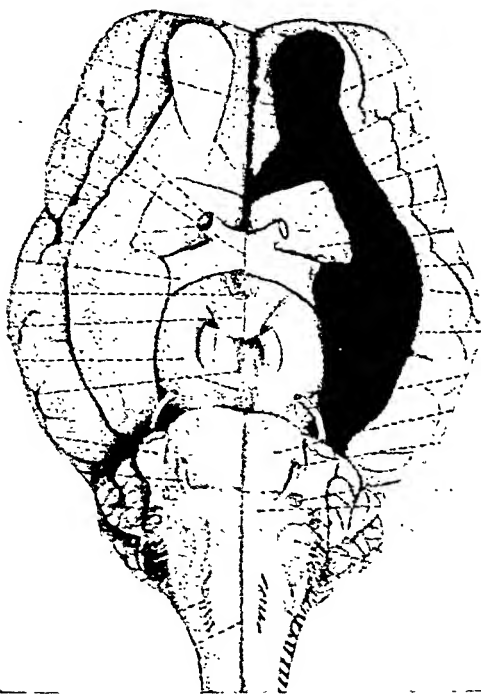


Fig. 249.—Brain of sheep showing large area (in black) for olfaction and taste.
(After Ranson.)

lobe giving the *reappearance in consciousness* of the *name or person* of a certain definite individual and then followed by a convulsive seizure. Again, and very important to the localization is the so-called *dreamy state* which at times takes the place of a full convulsive outburst. In one of our patients this dreamy state was as follows: the patient had attacks during which she would stare into space, then slide down into her chair,

preciated if one notes the large area present in the fetus of man (Fig. 252) as noted in the diagram. Now in the left temporal lobe appear the centers of speech so that a lesion of this area may produce in addition to any of the above features a disturbance of speech resulting in aphasia. One other feature

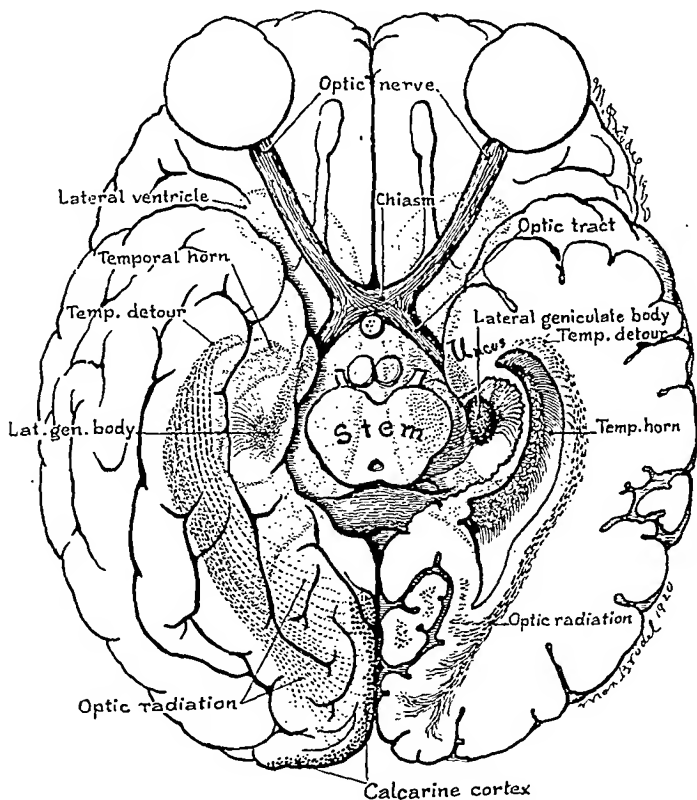


Fig. 253.—Inferior aspect of the pathway in transparency in the right hemisphere, indicating that the loop reaches as far forward in coronal section as the chiasm. In the left hemisphere the pathway is shown on section. (After Cushing.)

is of great importance of localizing value in temporal tumors or other lesions. This is defect in the *visual fields* and is explained by the relation of the optic radiations as they pass from the geniculate body to the calcarine cortex, out and around the lateral ventricle and through the temporal lobe (Fig. 253).

bulb and olfactory lobe which forms a considerable portion of the important structure of the brain. In reptiles and amphibia the olfactory *cortex* makes its debut superimposed like a cap over the primordial structures of the fish. In man the small olfactory bulb (Figs. 250, 251), the drawn out olfactory tract

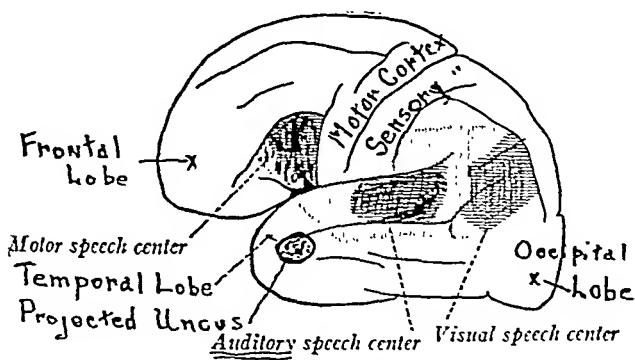


Fig. 251.—The cortical areas especially concerned with language.

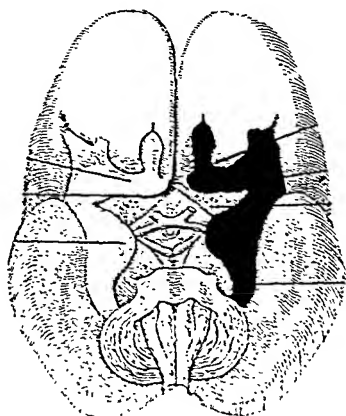


Fig. 252.—Brain of fetus showing comparatively larger area for olfaction and taste. (After Retzius.)

is elaborated into the uncus, gyrus hippocampi (taste), etc., all tucked up under and into the temporal lobe with the convolutions of the pallium covering all. The relative early importance of the olfactory area (and taste) which precedes in development that of the visual tract and centers may be ap-

summary shows 36 per cent with epilepsy, 50 per cent with mental symptoms, 31 per cent of left-sided tumors showing aphasia, 11 per cent uncinate attacks, 27 per cent with tinnitus, 17 per cent with deafness, 88 per cent of the tested cases showed visual field defects, 50 per cent showed hemiparesis, and 53 per cent showed cerebellar signs. Forty-two patients showed some degree of papilledema. Ocular findings occurred in 23 per cent in the sense of third nerve involvement and fifth nerve involvement also in 23 per cent. Ipsilateral dilatation of the pupil is of importance also as indicating the side of involvement. One other feature we should like to have present in our patient is a disturbance of taste but so far no conscious alteration has occurred.

I feel that in view of the typical clinical picture this patient has an organic defect present in the temporal lobe producing an uncinate epilepsy. While she is comparatively free of attacks on $\frac{1}{2}$ grain of phenobarbital three times daily and while ventriculograms as yet do not show enough alteration to warrant operation we shall watch this patient and her fits very carefully with the great probability that shortly the exact localization will be complete.

A tumor or other disturbance in this location may well cut into these radiations and produce small or large defects in the optic fields. These defects frequently take the nature of quadrant defects either in the upper or lower fields. A suggestion of such a defect is seen in the fields of our patient.

Summarizing the situation we have a patient who is well until the age of forty when she begins to have fits. These fits are of a specialized order. They start with an aura which is due to irritation of the focal area of the temporal lobe associated with olfaction, namely, the uncus, they are followed by an appearance in the zone of her consciousness of the name and person of a girl friend which represents a spread into the

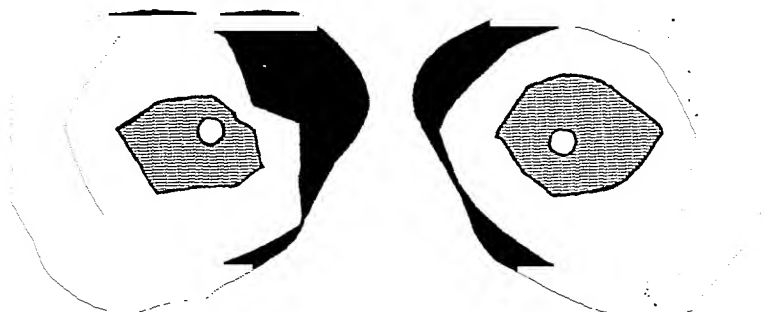


Fig. 254.—Visual fields in patient described in text.

larger temporal lobe, they are then followed by a major convulsion of usual epileptic form. Occasionally they are followed by a considerable period of loss of memory representing possibly the still disputed "higher center" of the temporal lobe or an interruption in frontotemporal association. Less often they are linked up with a soreness of the right arm and shoulder due to spread into the anterior lying sensorimotor convolution.

Recently Rowe has summarized the symptoms and findings in 52 cases of verified tumor of the temporal lobe. He quotes the significant remark of Oppenheim in 1899, "Wir haben niemals das Recht die Lokaldiagnose Tumor des rectem Schläfenlappens zu stellen." Fortunately not all of the temporal tumors are in the "recten Schläfenlappens." Rowe's

fluorescein was noted only for forty-eight hours when healing was complete. At the end of ten days the eyes and skin were practically normal. Lenses were prescribed for a hyperopic astigmatism with cycloplegia November 10, 1933.

On November 17, 1933, the left upper lid showed a marked chemosis. By the following day, the lids of both eyes were edematous. The globes were unaffected. The outgrowing lashes and eyebrows were again cut off and hot compresses resumed, this time, using ten per cent magnesium sulphate solution.



Fig. 255.—Edema seen at first visit.

As the condition grew worse, Dr. E. A. Oliver was consulted regarding the dermatological aspect and we placed the patient in St. Luke's Hospital, where she remained under treatment until December 30, 1933. In addition to the extensive dermatitis of the face, bullae appeared on the finger tips and a mild rash developed on the trunk, knees and lower legs, which did not show edema but caused much discomfort from the itching.

Hot compresses of aluminum subacetate (standard 8 per cent solution), 1 ounce per quart, were very effective in con-

CLINIC OF DR. FRANK BRAWLEY

ST. LUKE'S HOSPITAL

TOXIC EFFECT OF HAIR DYE ON EYES AND SKIN

REPORTS on the toxic effects of hair dye are rapidly accumulating. The usual picture is an intense dermatitis of the eyelids and surrounding skin with marked edema at times, extending over the greater part of the face and frontal region.

Later, there may be conjunctival edema with corneal ulceration and various types of keratitis, some so severe as to cause permanent blindness. There have been multiple small lid abscesses. Iritis has occurred. Undoubtedly, some of the cases must be classed as an allergic reaction, as in the instance of an attendant in a "beauty parlor" whose hands were affected whenever she applied the dye. In my own case, the first dye treatment produced no reaction.

The dye used is an aniline dye and probably paraphenylenediamine. Its effect takes place as early as two hours and as late as twelve days after use. Mild dermatitis of the eyelids without ocular involvement is very common and is due most frequently to cosmetics such as mascaro, the perfume in certain cold creams, astringent lotions, etc.

The patient I am presenting this morning, Mrs. T. S., was seen October 26, 1933, with marked edema and dermatitis of the eyelids with much pain and tenderness. Two days before this, Lash-Lure dye had been applied to the eyebrows and eyelashes.

The lashes and eyebrows were cut off with scissors as close to the skin as possible and constant hot boric compresses were used. The globes were protected with butyn and metaphen ointment.

The skin condition improved promptly, but on the fourth day a corneal ulcer appeared in the right eye. Staining with

trolling the edema. There was considerable pain about the face and frequent extensions and remissions of the dermatitis about the skin of the face. Various soothing ointments and creams were used, but the most effective was made up with equal parts of nupercaine "Ciba" ointment, 1 per cent, and zinc oxide ointment.

The eyes remained fairly quiet during the entire period in the hospital except for a recurrence of the corneal ulcer in the right eye on December 2nd, lasting three days. Only butyn



Fig. 256.—Shows less eyelid edema but extension to skin of face three weeks later.

and metaphen ointment were used to protect the eyes. At times there was moderate edema of the palpebral conjunctiva of both eyes. As the dermatitis of the eyelids was so persistent, the butyn ointment was stopped for a week and sterile vaseline substituted. This failed to relieve the dermatitis and the butyn was again used as it added greatly to the patient's comfort.

The condition is greatly improved although vision is not entirely normal, being 6/7.5 plus 2—left, and 6/10 right, with correction. The stereoscopic fields were normal.

diagnosis was acute cholecystitis with stones and beginning peritonitis.

The patient made a stormy convalescence but finally recovered and was discharged with slight drainage a month following operation.

Her third admission to the Evanston Hospital occurred on April 19, 1928, on the service of the late Dr. John H. McClellan, with Dr. R. T. Woodyatt as consultant. There was a definite history of polydipsia, polyuria and epigastric discomfort, which first appeared two weeks before admission. During the preceding year there were several attacks of abdominal pain and distention. Urine showed 0.319 per cent of sugar.

She was placed on a diet consisting of carbohydrate 79, protein 68, fat 140, with a glucose value of 132, representing 1848 calories, and given insulin, ten units morning and evening.

Further questioning of the patient elicited the information that her father had died of diabetes at forty-nine years of age. Her mother was living and well but weighed 200 pounds.

Dr. Woodyatt definitely advised against further surgical treatment at this time.

Her fourth admission on July 29, 1929, occurred on the service of one of us (G. de T.). In the interval there were several slight attacks, but two weeks previous to admission a very severe attack of upper abdominal pain developed. The patient had been sugar-free on a restricted diet, without insulin, until the attack two weeks previously. She stated that fat food and raw apples definitely distressed her. There was marked tenderness in the epigastrium and a vague mass was felt which was thought to be the pancreas (Fig. 257). This finding together with the history of previous attacks suggested an unrecognized acute pancreatic necrosis with gallbladder infection. The patient was operated upon and a hard mass was felt behind the stomach which seemed to fluctuate on deep pressure. The mass was located behind the posterior wall of the stomach to which it was firmly adherent. To the right it extended over to the midline and to the left it reached to the hilus of the spleen. The stomach was dissected up. An in-

CLINIC OF DRS. GEZA DE TAKATS AND G. KARL FENN

ST. LUKE'S HOSPITAL

THE EFFECT OF SURGICAL PROCEDURES ON THE SUGAR TOLERANCE OF DIABETIC PATIENTS. PRESENTATION OF FOUR CASES

WE are presenting four diabetic patients to illustrate the effect of various operations on their sugar tolerance.

Case I.—The first case is that of a white woman, age twenty-eight years, who was delivered with low forceps and episiotomy on February 12, 1927. There was no sugar in the urine at that time. On the sixth day after delivery an acute upper abdominal attack occurred and from then to the eleventh day a great deal of pain persisted over the gallbladder region. Her temperature during this period was normal and the white count did not rise at any time above 9000. She was discharged on the fourteenth day, feeling comfortable.

Her second admission occurred six weeks later, on March 26. In the interval the patient had had four attacks of upper abdominal pain accompanied by nausea and vomiting. Her abdomen at that time was distended. Urine examinations on March 27 and April 12 were negative for sugar, but on April 19 a faint, positive reaction for sugar was obtained. There was 0.52 Gm. of sugar in the twenty-four hour specimen.

On April 26 a surgeon performed a laparotomy and, according to the record obtained at the Evanston Hospital, a distended gallbladder with multiple stones was found. There was a considerable amount of hemorrhagic fluid in the abdominal cavity. The gallbladder was drained. The pathologic report showed the presence of fifteen cholesterin stones. No tissue was obtained for examination. The postoperative

tracted and without stones. Because of the length of the operation and the weakened condition of the patient no removal of the gallbladder was made. The abdominal wall was closed in layers. The anesthetic employed was ethylene and $\frac{1}{2}$ per cent novocain.

The contents of the cyst were examined for pancreatic ferments. They were negative for trypsin and diastase. The culture was sterile after four days.

Her recovery was smooth. The large tube was removed on the fifth day. She received 4000 cc. of fluid with 100 Gms. of carbohydrate intravenously and under the skin. She was dismissed from the hospital on the eighteenth day, with a small serous discharge. The sinus closed completely in six weeks. The patient was on a diet of carbohydrate 80, protein 63, fat 150, with a glucose value of 131; 1932 calories. She was gradually reducing the insulin from 20 to 5 units daily.

On January 29, 1930, she was entirely free of any complaints and was sugar-free without insulin. She had gained 7 pounds and in the course of six months her tolerance had markedly improved.

On August 17, 1933, she was admitted to the hospital for the fifth time. She had been perfectly well after the last operation until about February, 1933, when she began to have intermittent spells of nausea, vomiting and indigestion described as a heavy feeling in her stomach. About August 9 she began to have continuously increasing tenderness in the upper abdomen and on the 12th she had a severe attack of pain with distention. The bowels were fairly regular until this attack but there had now developed persistent constipation. The acute attack subsided but the continuous tenderness remained with some radiation to the right shoulder. There was no rigidity and no definite mass palpable except for a suspicion of a soft mass in the right upper quadrant. She was admitted to St. Luke's hospital with the idea of removing the gallbladder and exploring for a possible recurrence of the pancreatic cyst.

At operation done under ethylene anesthesia on August 19 there were dense fibrous adhesions in the upper abdomen.

cision was made in the gastrocolic ligament and the cyst was exposed. It was opened with a trocar and about 500 cc. of hemorrhagic reddish brown fluid was evacuated. The cyst was completely emptied and the cavity mopped out with



Fig. 257.—Mrs. E. C. The stomach is large, deformed and empties slowly. The pyloric half of the stomach on the greater curvature is displaced upward and toward the left. The duodenal curve is spread out over a larger area than usual. The stomach empties in eight hours.

sponges. Its wall was fairly smooth but occasionally small areas of fat necrosis were seen. A large tube was inserted in the cavity and the wall of the cyst was sewed to the peritoneum. The gallbladder was palpated and found to be small, con-

sisted and another severe attack occurred two years after the cyst was drained. A cholecystectomy was performed but no recurrence of the pancreatic cyst was found. The pancreas, however, was definitely hard and nodular. The patient is now on a restricted diet but needs no insulin. Her tolerance has been gradually rising during the last four months.

Case II.—The second case is that of Hazel H., nineteen years old, colored. The history has been previously reported.¹ Since the last report made nine months after operation further developments have taken place which are now presented, fourteen months after operation.

The patient was admitted to St. Luke's Hospital on October 17, 1932. Her great grandmother died of diabetes. Aside from infrequent abdominal cramps at the age of twelve and fifteen years and the customary infectious diseases of childhood, she was quite well until January, 1932, when polydipsia and polyuria set in. At the end of March, 1932, because of frequent colds a tonsillectomy was done, following which she went into diabetic coma. She was then admitted under the care of one of us (G. K. F.) and 235 units of insulin were given during the first fifteen hours together with glucose, fluids and caffeine. She was finally discharged on a diet of carbohydrate 100, protein 60 and fat 175, with a glucose value of 151, representing 2311 calories. Thirty-five units of insulin were given in the morning and 25 units at night.

During the interval between discharge from the hospital and readmission she was infrequently observed in the outpatient department. Because of her financial circumstances, diabetic regulation even on this dose of 60 units of insulin was insufficient. Her preoperative status is described in detail in the previous communication. At this time we shall just state that her diet consisted of carbohydrate 75, protein 50, fat 150, glucose value 120, covered with 40 units of insulin.

Further preoperative studies revealed that ergot definitely

¹ De Takats, G., and Fenn, G. K.: Bilateral Splanchnic Nerve Section in a Juvenile Diabetic, *Ann. Int. Med.*, 7: 422-430, 1933.

The gallbladder wall was thick, the pancreas hard and nodular. There was no evidence of any recurrence of the cyst. The gallbladder was removed. The common duct was not distended and was not explored. The postoperative diagnosis was adhesive peritonitis, chronic cholecystitis and chronic pancreatitis.

The histology of the gallbladder showed fibrous changes in the lining and deeper portions of the wall and in these fibrous tissues disseminated collections of lymphocytes, plasma cells and eosinophilic leukocytes were found.

The patient made an uneventful recovery.

Because of the presence of a chronic pancreatitis found at operation it was thought advisable to place the patient on a low fat diet. Consequently she was placed on a diet of carbohydrate 100, protein 60, fat 40. While immediately after operation she required a considerable amount of insulin, it was possible to discharge her on this diet without any insulin. She was discharged August 31, 1933.

At examination on October 25, 1933, the patient was able to increase her diet to carbohydrate 120, protein 60, and fat 40 and was sugar-free without insulin. A fasting blood sugar determination made during this interval revealed 143 mg. on September 14 and 155 mg. on September 29.

The patient was last seen on January 14, 1934. She was sugar-free on a diet of carbohydrate 110, protein 67 and fat 110 with 147 Gm. of available glucose.

Comment.—This patient with a history of diabetes in her family, had no clinical evidence of such a disease until a sudden abdominal attack occurred a week after delivery. While not recognized at the time and though operated on for acute cholecystitis, she undoubtedly had an acute pancreatic necrosis following delivery. Diabetes resulted and was treated, as stated, by expert medical management. Two years later because of intermittent abdominal colics and a vague mass in the epigastrium she was explored and a large pancreatic pseudocyst was drained. The gallbladder was not removed because of her precarious condition. Following this operation her tolerance markedly improved. However, colicky pains per-

was quite stable on this régime and there were no marked fluctuations as occurred previous to operation. The patient's insulin sensitivity rose; in fact, the same dose of insulin administered after operation produced a rapid fall in blood sugar and an inability to regain the level within two hours.

Five months after operation the patient married without our knowledge and became pregnant. Her insulin requirement did not rise during the first five months of pregnancy. At this time she broke her diet and also her insulin syringe, became drowsy and aborted. The CO_2 combining power

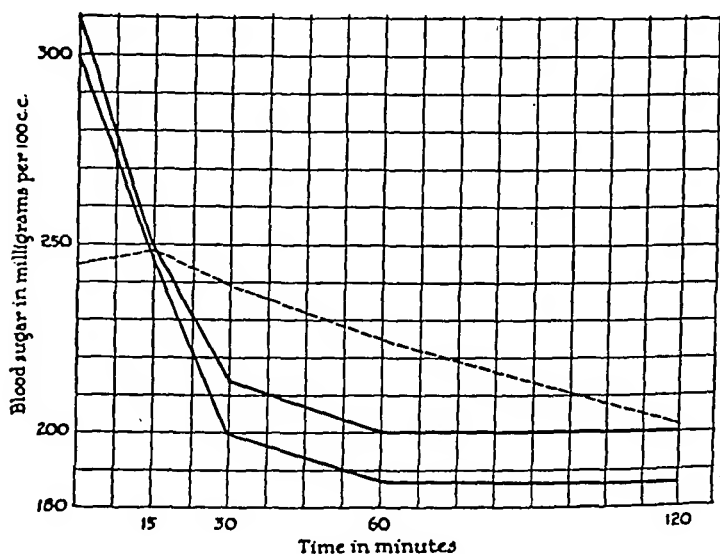


Fig. 259.—Insulin-sensitivity test. Interrupted line: before operation; straight lines: one and two months after operation.

dropped to 16 per cent. Sixty units of insulin given in the first twenty-four hours brought her out of the coma from which she recovered completely. She was discharged again on the original diet with 25 units of insulin.

At the present time, fourteen months after operation, the patient's diabetes is considered mild and easily controllable. Because of the difficulty of obtaining a proper diet the actual gain in tolerance is difficult to determine. However, attacks of cold from which she suffers frequently will not require an increased amount of insulin.

depressed the galactose tolerance curve (Fig. 258). This was interpreted as a sign of increased sympathetic irritability of the sugar-secreting mechanism.¹ The insulin sensitivity test was determined and showed that when one tenth of a unit of insulin per kilogram of body weight was given intravenously very little fall of the blood sugar level occurred within the next two hours. A discussion of these two tests will be made under the Comments.

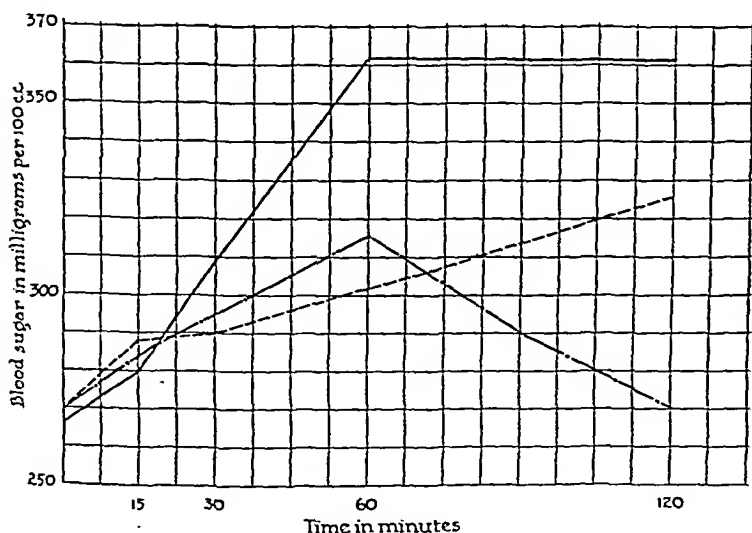


Fig. 258.—Galactose-hyperglycemia curve. For details of this test see April, 1934, number of the *Annals of Internal Medicine*.

On October 22, 1932, under ethylene-novocain anesthesia a supradiaphragmatic and retropleural approach was used to cut the left major and minor splanchnic nerves. The post-operative convalescence was uneventful. On November 12, 1932, three weeks later, the right splanchnic nerves were exposed and severed. The results of the bilateral splanchnic section on the diet and insulin requirements were as follows. On the same diet the daily insulin requirement dropped to 20 units. The glucose-insulin ratio rose from 3:1 to 6:1. She

¹De Takats, G., Fenn, G. K., and Trump, R. A.: Splanchnic Nerve Section in Juvenile Diabetes. I. Selection of Cases for Operation, *Ann. Int. Med.*, 7: 1201, 1934.

revealed very little change after operation. Compared with his preoperative requirement of 65 units of insulin, 50 to 55 units are required daily. There was practically no change in the reaction to insulin. His tolerance was stable and the only appreciable gain seemed to be the omission of the noon dose of 20 units. At present, five months after operation, the patient's condition is practically unchanged.

Comment.—A second juvenile diabetic patient was subjected to bilateral splanchnic nerve section with practically no gain in tolerance. This patient markedly differs from the one previously described, in that he was sensitive to insulin and responded only slightly to ergot. In a case of this type suppression of the sympathetic impulses to the liver, pancreas and adrenals did not accomplish any gain in tolerance.

Case IV.—Frank H., age twenty-four years, a severe diabetic, was admitted to St. Luke's Hospital on September 5, 1933. He first noticed diabetes six years ago with a gradual onset of polydipsia and polyuria. Three years ago he complained of sweating, restlessness and nervousness. He was admitted to the Cook County Hospital where a thyroidectomy was performed. He was improved until six months before admission when symptoms identical to those previous to thyroidectomy returned. He stated that his basal metabolism was 65 per cent previous to thyroidectomy.

The patient was observed in the out-patient department by both of us and our first attempt was to bring down his basal rate of $+45$ per cent with Lugol's solution. This was accomplished quite easily. Subsequent determinations showed a basal metabolism rate of $+24$ per cent on July 1, 1933; $+10.8$ per cent on July 21, and $+12.9$ per cent on August 4.

While the administration of Lugol's solution produced a marked clinical improvement at first, it did not seem to relieve the symptoms later and his restlessness and tachycardia recurred. After the administration of Lugol's solution tests were run for insulin sensitivity and for a response to ergot. They are shown in the accompanying chart (Fig. 260). These tests

Comment.—Bilateral splanchnic section was performed on an eighteen-year-old diabetic girl for the purpose of stabilizing and increasing her sugar tolerance. There has been an immediate drop to one half of her previous insulin requirement which seems to be due to an increase in insulin sensitivity (Fig. 259). The insulin sensitivity test reported twelve months after operation shows that this change is still persisting. A final report will be made several years hence.

Case III.—The third case is that of Joe D., a sixteen-year-old white boy, who was admitted to St. Luke's Hospital on July 5, 1933, with a diagnosis of a severe type of juvenile diabetes with gradual onset. He has had measles and tonsillitis in the past, and a tonsillectomy in February, 1933. His mother is obese and a diabetic.

He was in perfect health until September, 1932, when he began to lose weight and noticed a progressing weakness and polyuria. He was admitted twice in coma to other hospitals in the city, and has had three further attacks of acidosis in the last three months previous to admission. At admission there were badly decayed teeth which were taken care of by Dr. F. W. Merrifield. The thyroid isthmus was palpable. There were no palpable or x-ray evidences of vascular changes. The diaphragms moved freely. He was fairly sensitive to insulin and ergot depressed the galactose hyperglycemia curve but not to a marked degree. His preoperative diet was carbohydrate 75, protein 60, fat 150, with a glucose value of 125 and 1890 calories. The insulin requirement was 30–20–25 and the glucose-insulin ratio was 1.6.

On July 12, 1933, a resection of the left splanchnic nerves and thoracic sympathetic chain was done. The right side was operated on twelve days later. A smooth postoperative convalescence followed both operations. The patient was discharged on the preoperative diet with 55 units of insulin given twice a day. He regained his preoperative weight in two months. The glucose-insulin ratio rose from 1.6 to 2.7. Observations on the insulin sensitivity and galactose tolerance

to St. Luke's Hospital on December 9, 1933, for bilateral splanchnic section. The results of this operation will be presented at a later time.

Comment.—We are dealing here with a patient who had a severe juvenile diabetes associated with hyperthyroidism. At the same time he showed marked indications of an increased sympathetic irritability and insulin-resistance. Removal of the thyroid factor and return of the basal metabolism rate to normal enabled us to decrease the insulin requirement, but his original characteristic tendency to sympathetic impulses still persisted. Splanchnic nerve section on this patient should reduce the insulin requirement to a lower level. Since this report went to press, the operation has been performed resulting in a reduction of the insulin requirement from 55 to 10 units. This result has been maintained for four months so far.

Conclusions.—These four cases while entirely different in character emphasize the following points:

1. A diabetic patient in whom a positive diagnosis of cholecystitis or particularly pancreatitis can be made is greatly benefited by a removal of the infectious focus and by a decompression of the pancreas. Such a diabetic in the presence of proved pancreatic pathology has a good change of improvement because of the marked regenerative power of the pancreas.

2. The average juvenile diabetic whose tolerance is poor and very unstable may show a poor response to insulin and give a response to sympathetic suppression (ergot). In such a case section of the splanchnic nerves will make a diabetic patient more sensitive to insulin and improve the alimentary hyperglycemia curve. The tolerance becomes stable. This operation, however, would seem ineffective in a patient who was sensitive to insulin and responded poorly to ergot. This experience emphasizes the importance of these tests previous to operation.

3. A patient with marked hyperthyroidism which recurred after extensive operation was subjected to a second thyroidectomy. His insulin requirement dropped and his tolerance became more stable.

revealed an abnormal sympathetic hyperirritability which made him appear suitable for splanchnic section. It was thought wise, however, to eliminate the thyroid factor first and therefore on September 19, 1933, a subtotal thyroidectomy was performed by Dr. T. L. Hansen. Very little glandular tissue was found, not more than 2×3 cm. on the right side, and a tiny bit of tissue, the size of a small pea, on the left side. These were resected down to the posterior capsule of the gland.

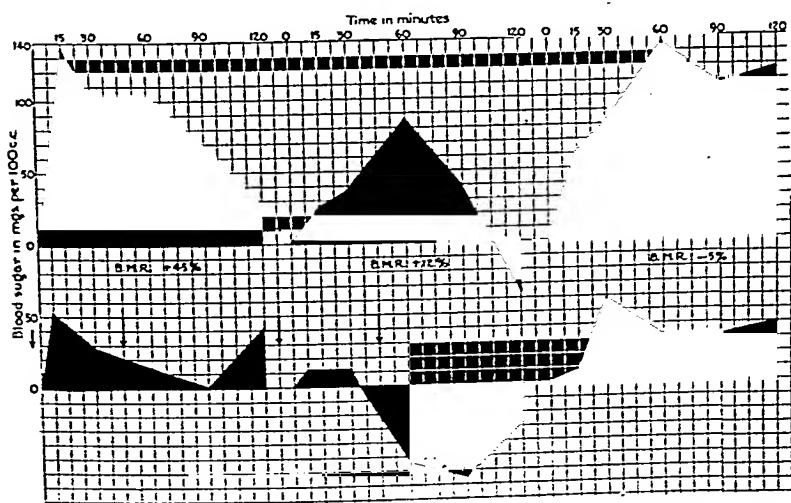


Fig. 260.—Galactose hyperglycemic curves during hyperthyroidism, after control with Lugol's solution, and after thyroidectomy. Note the marked suppression of galactose-hyperglycemic curve by ergot, particularly in the middle column where a reversal of the hyperglycemia took place.

The patient made an uneventful recovery and his preoperative dose of insulin, 30–15–25, could be reduced after operation to 30 units before breakfast and 25 before the evening meal. He was discharged on a diet of carbohydrate 80, protein 60, fat 150.

The improvement in the patient's diabetes can hardly be expressed by a reduction of 15 units of insulin. As he became far more stable and rapidly put on weight he was again studied for insulin sensitivity and ergot response. He was readmitted

These cases indicate that there may be different types or at least different manifestations of diabetes mellitus. Disturbance in carbohydrate metabolism while it may be due occasionally to pancreatic damage is conceivable as an instability of counter-regulation or opposition to insulin. Of the experimentally and clinically recognized factors, the pituitary, thyroid and adrenal glands may be mentioned as capable of opposing insulin action. Such a diabetes then is due to an imbalance between the opposing forces and not necessarily to diminished insulin secretion.

negative for albumin, sugar, casts and red blood cells. Blood examination showed 4,200,000 red cells and hemoglobin 65, with no nucleated red cells. She had no headache, visual disturbance, or gastric discomfort. There was no epigastric tenderness, and the uterine fundus was palpable almost a hand's breadth above the symphysis.

A glance at the accompanying chart will show that there was no essential variation in the blood picture of this patient

BLOOD PICTURE FROM BEGINNING OF SECOND TRIMESTER TO DELIVERY

Month of pregnancy.	Red cells.	Hemoglobin.	Reticulo-cytes.	Color index.
Fourth.....	4,200,000	65		
Fifth.....	4,200,000	65		
Sixth.....	4,000,000	62		
Seventh.....	3,600,000	60		
Eighth.....	2,200,000	30	2.2	
Ninth.....	2,200,000	20	3.2 3.4	0.4

Medication

Fourth, fifth, and sixth months.	Seventh month.	Eighth month.
Blaud's pills, 50 grains daily. Various liver extracts. High protein diet.	Iron citrate, 15 grains, four times daily. Liver extract. Dilute hydrochloric acid.	Iron citrate, 30 grains, four times daily. Liver extract intramuscularly by mouth. Dilute hydrochloric acid.

from the first examination in May until between the seventh and eighth month, when the hemoglobin dropped from 60 to 30, and the red cells from 4,200,000 to 2,900,000. With this alarming fall in hemoglobin the patient entered the hospital for observation on September 17, and the following additional

CLINIC OF DR. HAROLD K. GIBSON

ST. LUKE'S HOSPITAL

MICROCYTIC HYPOCHROMIC ANEMIA WITH PREGNANCY

IN presenting this patient, it is with a full realization that certain clinical data desirable for more conclusive deductions are lacking, yet the infrequency of anemias of this type and severity in pregnancy is, I believe, ample justification for the presentation of this patient with the data available.

The patient is a white woman, thirty-three years of age, gravida III. Her mother died of pulmonary tuberculosis at the age of thirty-two. Her first pregnancy occurred in 1925. At about the seventh month she was sent to a hospital by her physician because of high blood pressure, edema, severe headaches, with marked visual disturbance and albuminuria. She had repeated convulsions. Following a bag induction she was delivered of a 3½ pound infant which survived six months.

Her second pregnancy was in 1927. At the sixth month she developed hypertension with albuminuria. She was sent to the hospital for observation and eliminative treatment, in the course of which spontaneous labor ensued and she was delivered of a stillborn infant. During both pregnancies she had been on a meat-free diet. Following the last pregnancy she was given injections of iron by her physician for "poor blood."

The third pregnancy began in 1933 and she presented herself for the initial examination on May 18. She weighed 136 pounds. There was moderate pallor of the skin. No edema of ankles or eyelids was noted. Teeth were good and tongue appeared normal. Lungs were negative. Heart was not enlarged to percussion, and there was no accentuation of sounds. Blood pressure was 110 systolic and 70 diastolic. Urine was

observation because of a previous eclampsia and hypertension, and living under ideal environment. From her first examination on May 18 she was on a generous protein diet including red meats, supplemented by Bland's pills, 50 grains, daily and the various liver extracts. In placing the patient upon a high protein diet from the first trimester of pregnancy, I was influenced not only by the then moderate anemia but from the conviction that a low protein diet in the preeclamptic toxemias of pregnancy is without merit. Blood pressure readings and urinalyses were made at ten-day intervals with the understanding that at the first evidence of hypertension or renal insufficiency, the pregnancy would be terminated irrespective of the period of gestation. Beyond an occasional trace of albumin and rise in blood pressure to 140/70 a few days prior to delivery, there was no evidence of a recurrence of the hypertension.

While it must be conceded, as suggested by Dr. N. C. Gilbert who saw her during her first observation period here, that a more liberal dosage of iron earlier in her pregnancy might have given improvement in her blood picture (all of the 3 cases reported by Strauss¹ showing a definite improvement under iron), it is my personal conviction that the pregnancy *per se* was the determining factor in this patient, and as in the majority of the more severe toxemias of pregnancy, definite improvement begins only with the termination of the pregnancy. That the pregnancy was the determining factor is evident from the following clinically demonstrable facts.

First, upon the date of her initial examination, when she was approximately nearing the end of her first trimester, there was no evidence of a severe anemia, red cells being 4,200,000 and hemoglobin 65.

Second, what Whitby² so aptly described as "the sudden, dramatic and alarming fall in red cells" from 4,000,000 to 2,220,00 and hemoglobin from 60 to 20 in the last trimester when the fetal depredations of iron are at the maximum, occurred under ideal home environment with a more than generous protein diet supplemented by what was deemed an adequate

amount of iron and various preparations of liver extract. I wish to emphasize that for a period of ten days before the rupture of the membranes this patient was receiving 120 grains of iron citrate daily, liver extract by mouth, and two intramuscular injections of liver extract, and in spite of this there was a final drop in hemoglobin from 30 to 20.

Third, the marked and immediate remission following delivery, when the hemoglobin rose from 20 to 45 in fourteen days.

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PATHOLOGIC CLINIC OF DR. EDWIN F. HIRSCH

ST. LUKE'S HOSPITAL

CRYPTIC BRONCHIOGENIC CARCINOMA OF THE LUNG

THE symptoms of a patient with a disease unfold themselves to some conclusion in a fairly orderly sequence. The accumulated notations of these sequences of symptoms in patients and the technic of isolating or identifying specific causal agents or factors, finally stamp diseases as entities. By a comparative process of reasoning, symptoms singly or in groups, in a patient constitute the basis for diagnosis. This matching of a disease pattern in diagnosis with established standards becomes involved when the symptoms of a disorder in a patient seem strange or conflicting because of some unusual process of evolution.

The problem in diagnosis then stimulates a search for data akin to the ferreting necessary to uncover the essentials of a mystery. Recourse is taken to known means available, roentgen and laboratory, in order to obtain this information. Sometimes all of these efforts yield only a modicum of information, and the final classification of the disease is obtained by a thorough examination of the body and a histologic study of the tissues after the death of the patient. Disorders difficult to diagnose are encountered in patients with a small primary carcinoma, commonly bronchiogenic, in whom the initial focus remains silent and the metastases arouse symptoms for which the patient seeks relief. The illness of these patients is protracted, the kaleidoscopic manifestations in one or several parts of the body, of the same general character or different, arouse the greatest curiosity and urge the imagination into speculative ideas, seeking to correlate logically the symptoms and data obtained with some one disease entity. Several of

these diagnostic problems have been recounted in publications.¹ Others remain fragmentary in our records, or eventually have been clarified by postmortem examinations. Another recently has been unraveled by postmortem examination after a careful clinical study.

A white woman, aged fifty-nine years, entered St. Luke's Hospital on March 10, 1933, in the care of Dr. Arthur R. Elliott. She had had intermittent sharp pains in the left side of the neck for five months, aggravated by rotation of the head, and occasionally radiating down into the left side of the back. There were several small firm left supraclavicular and sub-maxillary lymph nodes. The lungs had no significant changes.

A roentgen examination of the cervical portion of the spine by Dr. E. L. Jenkinson on March 13, 1933, demonstrated a destructive lesion of the fourth cervical vertebra, extending through the superior and inferior articular surfaces. By June, the fifth and sixth cervical vertebrae were involved and possibly the ribs. On August 31, 1933, the right leg and foot became edematous and painful, and in November there was edema of the right upper extremity. The erythrocytes of the blood were 3,180,000 and the leukocytes 12,900 per cmm. The urine had a few leukocytes and a trace of albumin. The Wassermann reaction of the blood was negative. The clinical diagnosis of metastatic carcinoma of the cervical vertebrae was made, the primary growth not having been found. The patient grew weaker, became more and more emaciated and died the evening of December 16, 1933, about fourteen months after the first manifestation of her illness.

The essentials of the anatomical diagnosis of the postmortem examination are: Small verrucous bronchiogenic carcinoma of the right lung; metastatic carcinoma of the fifth, sixth and seventh cervical vertebrae, and of the calvarium, ribs, pleurae, lungs, parabronchial and axillary lymph nodes; marked emaciation; obturating thrombus of the inferior vena cava and of the right and left common iliac veins; bilateral hydrothorax; ascites; hydropericardium; senile arteriosclerosis of the aorta

¹ Hirsch, Edwin F. and Ryerson, E. W.: Arch. Surg., 16: 1-30, 1928.

and of its main branches; slight fatty changes of the right coronary artery; fibrous changes of the leaflets of the tricuspid valves, etc.

The tissues of the head, neck and trunk were examined but only the essentials of the autopsy record are mentioned here. The emaciated body was 150 cm. long and weighed 90 pounds. The right pleural space contained about 1000 cc. of faintly turbid yellow fluid, the left about 500 cc. There were no pleural adhesions on the right side and only a few at the base on the left. The right lung weighed 300 Gm. The pleural surfaces were glistening, gray and covered with many discrete and confluent opaque, gray white nodules, pinpoint to 2 mm. in diameter and about 1 mm. thick. The margins of the lung lobules on the pleural surfaces were traced by fine linear milky opacities. At the inferior margin of the right lower lobe behind and near the medial edge was a retracted stellate scar 2 cm. in diameter. A mass of friable granular, gray red lung tissue beneath this was 2.5 cm. in diameter. The divisions of the right bronchus, opened into their smallest ramifications, contained a small amount of frothy secretion. The lining was gray and in the usual longitudinal folds except a finely granular, slightly thickened plaque 1.0 by 0.5 cm. on the ventral surface of the second division of the main bronchus extending into the lower lobe. A few centimeters beyond, this division extended into the necrotic nodule in the base of the lung. The inside circumference of this bronchus was 1.5 cm. The left lung weighed 365 Gm. The pleural surface had gray nodules and linear milky patches like in the right. The lower lobe and lower half of the upper lobe had regions of bronchopneumonia. The divisions of the left bronchus opened into their small ramifications, contained a viscid secretion. The lining was gray, slightly hyperemic and in the usual longitudinal folds. Both lungs had a diffuse growth of interstitial fibrous tissue.

The calvarium had three osteoplastic metastases, one near the midline on the left side just behind the coronal suture, 2 cm. in diameter, another in the right temporal bone 3 cm. in diameter, and the third seen only on the inside near the center.

of the sagittal suture, 2 cm. in diameter. These protruding tissues were firm and red gray. The right eighth rib had a fusiform thickening 3 cm. in diameter that began 8 cm. from the spine; the left seventh rib in about the same position had a nodule 2 cm. in diameter. A friable mass of granular bone tissue $8 \times 7 \times 3$ cm. was fused to the left side of the fifth, sixth and seventh cervical vertebrae. The axillary and parabrachial lymph nodes were slightly enlarged and contained firm gray tissues resembling tumor metastases.



Fig. 261.—Photomicrograph illustrating the tissue structures in the subpleural nodules. Note the small groups of carcinoma cells and the abundant growth of scar tissues. ($\times 179$.)

The warty thickening of the bronchial lining and the friable tissues in the lower lobe were infiltrated by small masses of carcinoma cells accompanied by a marked scar tissue reaction. The tumor cells were medium in size and were arranged closely together in a mosaic pattern. The lymph channels of the lungs were markedly invaded by carcinoma cells and occasionally small groups of these cells formed short blunt papillae or bizarre tubules. The extensions of these carcinoma tissues in the lymph channels reached to the pleural surfaces of the

and of its main branches; slight fatty changes of the right coronary artery; fibrous changes of the leaflets of the tricuspid valves, etc.

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growth of scar tissue. The parabronchial and axillary lymph nodes (Fig. 262) had tumor metastases. The bone lesions had metastatic carcinoma and an osteoplastic tissue reaction (Fig. 263).

The notable feature of the clinical progress of this patient was the insidious onset of symptoms caused by metastases into the osseous system from a small bronchiogenic carcinoma of the lung. The primary tumor, a small warty thickening of the lining of a second division of the bronchus did not cause clinical symptoms and remained hidden until demonstrated by a postmortem examination. These small primary bronchiogenic carcinomas of the lung easily escape notice in routine postmortem examinations. The tumor cells invade extensively the lymph channels of the lungs and on the pleural surfaces form, with fibroplastic tissues, the opaque gray tracings of the lobule margins and the multiple small nodules. The tumor cells in the soft tissues provoke a scar tissue reaction and in the osseous system a growth of bone.

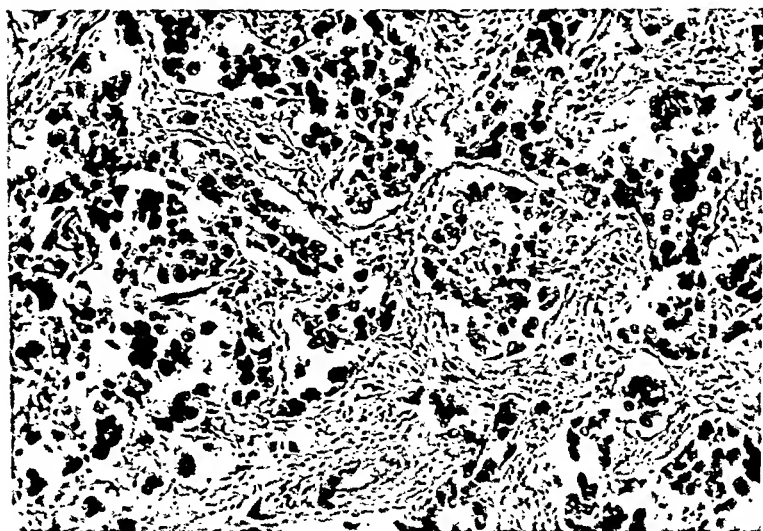


Fig. 262.—Photomicrograph illustrating the tumor tissues metastatic in the axillary lymph nodes. ($\times 179$.)

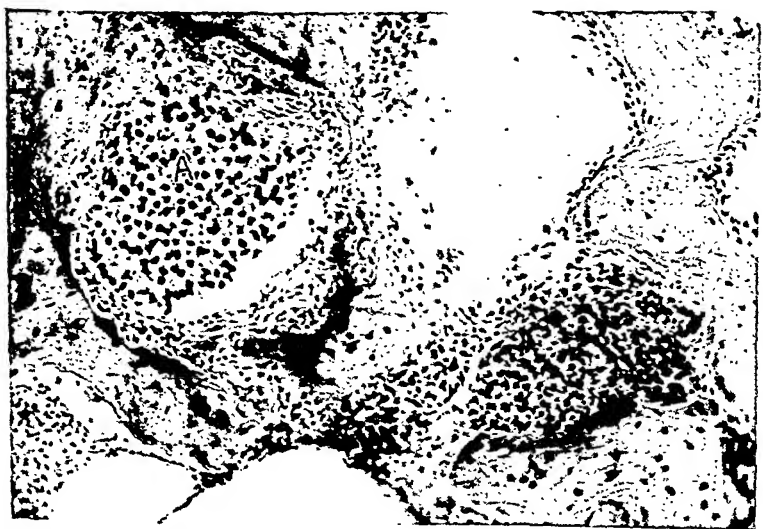


Fig. 263.—Photomicrograph of the bone tissues with metastatic carcinoma (A). ($\times 179$.)

lungs and the nodules (Fig. 261) and milky opacities noted on the pleurae were tumor cells accompanied by a marked

five months ago, when he presented the symptoms listed above, no worse than they were at their onset thirteen years ago, and with no additional complaints.

Physical examination was essentially negative, except for tenderness over the lumbosacral region, right sacro-iliac joint and pain on bending the back and on forced flexion of the right hip. There were no visible or palpable deformities.

Blood examination showed a red blood count of 5,050,000, white blood count of 10,000, hemoglobin 83 per cent, blood



Fig. 264.

calcium 9.6, blood phosphorus 3.3, and negative Wassermann and Kahn tests. The urine was and is now essentially negative, including a negative Bence-Jones reaction.

α -Ray examination revealed the nature of the disease as a disseminated or polyostotic Paget's disease. It showed advanced changes in the sacrum, all of the pelvic bones, lumbar spine, femora and skull (Figs. 264, 265), with less marked changes in the humeri, tibiae and radii. No changes in the other bones could be made out by radiological examination.

CLINIC OF DR. HAROLD I. MEYER

ST. LUKE'S HOSPITAL

PAGET'S DISEASE (OSTEITIS DEFORMANS)

THE patient I am presenting this morning is a white male, forty-six years of age, who complains of symptoms of pain in the lumbosacral region and in and about the right hip. He gives a history of pain intermittent over a period of thirteen years, varying somewhat in location and character, but always referable to the lower back and right lower extremity. At the beginning it was most severe in the lumbosacral region and right hip, but soon included the right knee and followed the course of the right sciatic nerve. Extraction of his teeth was advised, following which he had a year of relative comfort. Ten years ago, following an exacerbation of severe pain in the back, right hip and knee, his tonsils were removed.

x-Ray examination of his lumbar spine, sacrum, pelvis and femora was made in 1925 by a competent radiologist, who noted that "there is a very peculiar condition in the pelvis and head of both femurs—both show a high grade of sclerosis, slightly more in the region of the sacro-iliacs, so that it looks porous. I do not know what this is. The sclerotic appearance with real breakdown is almost sure to be metastasis from carcinoma. . . ."

The patient was then very carefully studied, with particular reference to the genito-urinary system, without finding evidence of primary malignancy.

This man has continued to work, with exacerbations and remissions of these symptoms almost every day up until the present time, without developing any deformities, without loss of weight or strength, or any new symptoms. I first saw him

tion of the osteogenic marrow connective tissue. This condition progresses throughout the bone, finally setting up a periosteal irritation with proliferation of new bone. This can rarely be seen on x -ray examination, since the new bone is converted into diseased bone as rapidly as it is produced. It was *formerly thought that here no periosteal proliferation existed*, hence its absence was used in differentiating it from lues and tuberculosis, which are characterized by periosteal proliferation. The disease goes on to sclerosis which is a healing process. This process in turn may go on to produce sequestra. No true bone cysts or giant cell tumors, such as found in von Recklinghausen's disease, are seen in Paget's disease. Instead there are spaces filled with fatty marrow or areas of liquefaction of connective tissue or necrosis.

This disease usually occurs clinically after the age of forty years, and is more common between the years of sixty and seventy. Disseminated or polyostotic Paget's disease of which this is a type is relatively rare and Jaffé¹ estimates that no more than 500 cases have been reported up to the present time. Carman and Garrick² recorded 15 cases from among 237,000 admissions to the Mayo Clinic.

In those cases where no deformity exists, the diagnosis is made largely on the x -ray findings, which are most pronounced in the ilia, sacrum, lumbar vertebrae, femora and calvarium. In this patient the x -ray findings are typical.

The prognosis in this case in regard to life is good, life expectancy not being reduced. Whether or not he will develop deformities cannot be predicted. Sarcoma of the bone seems to be a frequent complication in the disseminated type of Paget's disease, in which group this case falls. Bird found 7 cases of bone sarcoma in 64 recorded cases of polyostotic Paget's disease in four large Boston hospitals.

The treatment is unsatisfactory since we have no known remedy which will cure or even check the disease. Calcium and viosterol have been employed with questionable results.

¹ Jaffé: Arch. Path., 16: Dec., 1933.

² Carman, R. D. and Garrick, W. M.: Jour. Radiol., 2: 7, April, 1921.

He was placed on treatment consisting of calcium gluconate and cod liver oil by mouth, with salicylates as indicated to make him comfortable. For three months he was practically free from pain, but within the last month he has had an attack as severe as any he can recall.

It is obvious from an examination of this patient that this disease can reach an advanced state without deformity, hence the name osteitis deformans is a bad one, and the terminology, "Paget's disease," may well be retained.

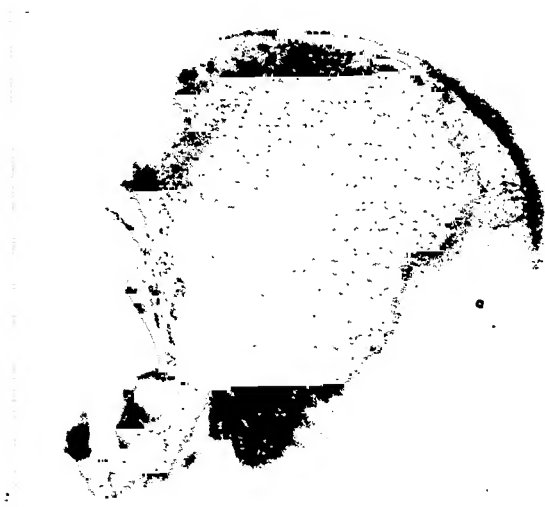


Fig. 265.

The etiology of the disease is unknown but many theories have been advanced, ranging from heredity, infection, endocrine or vitamin imbalance. Nor is the exact nature of the disease understood. There exists a breaking down of normal bone structure with replacement of new bone, more porous in structure, and the proliferation of this new, weaker than normal is probably a compensatory mechanism. It is thought by some that this disease represents a disturbance of the normal mechanism of bone replacement that is constantly going on.

There is some initial force which causes absorption of bone, with a secondary reaction of the bone marrow; with prolifera-

use the leg without pain. The arthritis then developed in the shoulder joints, the hands and the right leg at various times, some joints improving while the arthritis was developing in other joints. During the last few months the arthritis has been almost absent in the arms, hands and legs. He has never had fever with this condition and he worked regularly throughout the last two years; often working when the knee joints or other joints were swollen to at least twice their normal size. The pain accompanying the arthritis has been worse during wet, cold weather.

On the 19th of July—about seven weeks ago, patient slipped and fell in such a way as to strain his right hip and cause it to be very painful. He was able to use the right leg but it caused him considerable pain; so he walked with crutches or a cane most of the time since the accident. Occasionally the pain in the right hip has been so slight that he was able to walk without a cane.

During the last two years he has had extensive treatment for arthritis by heat and electrical devices, and by light. He also had some "joint-cracking" manipulations by a doctor in Toledo, and these gave him definite relief.

On October 1, six days ago, the patient was walking across the floor in his son's home when the right leg collapsed under him, being accompanied by a loud cracking sound as if a large bone had broken. He was unable to stand on his right leg, but with the aid of crutches he walked unaided down a stairs and out of doors to get into his automobile. He had very little pain. He intended to go home but his son insisted upon his going to the doctor's office for an x-ray examination. He walked with crutches to the doctor's office where x-ray films were made. He sat in a chair while there for over an hour waiting for the physician to come. A fracture was found in the femur and the limb was splinted before he went home. The next day the physician brought a specialist to his home who examined him and then advised immediate amputation of the right leg at the hip. The patient would not consent to this and came to Dr. Plummer at his office for advice.

CLINIC OF DRS. EDWARD L. JENKINSON AND
J. M. FOLEY

ST. LUKE'S HOSPITAL

AN INTERESTING STUDY OF BONE LESIONS WHICH
PROVED TO BE MYELOMATA

THE patient we are presenting is of interest especially from the standpoint of the differential diagnosis. For over two years we have observed the patient, and at no time have we been able to definitely classify the bone lesions which have developed from time to time.

In February, 1932, we obtained a biopsy from his right femur and even then we were not convinced of the exact nature of the lesion. The fact that the different lesions appeared at long intervals also made the diagnosis difficult.

To add to our confusion, the lesions responded exceptionally well to roentgen therapy. The later lesions seemed to be more susceptible to irradiation than the first. While the first lesion discovered, which was in the right femur, did not progress after roentgen therapy, it did not greatly improve, that is, there was not the definite bone regeneration which can be demonstrated in the jaw.

The patient, a white male, aged fifty, well nourished, was admitted to the hospital as a patient of Dr. Samuel C. Plummer, with the following complaints:

1. Inability of use of the right leg—six days' duration.
2. Chronic arthritis of joints of all extremities—two years' duration.

Present Illness.—Patient has had arthritis for about two years which began first in the left ankle and left knee, which joints were greatly swollen. In the mornings when he arose he would find the joints very painful and it would take sometimes a few hours to get the joints loosened up so he could

Head: Eyes—Conjunctiva negative. Pupils react to light and accommodation.

Mouth—Most of the lower and all of the upper teeth have been extracted. The lower teeth present are in poor condition.

Fauces negative; no inflammation about tonsils.

Chest.—Lungs normally resonant; expansion good and equal on the two sides. No altered fremitus; no râles. Breath sounds normal. Heart not enlarged; no murmurs or arrhythmia.

Abdomen.—Moderately flaccid. No areas of tenderness or palpable masses. No fluid present. Liver, kidneys, spleen not palpable.

Extremities.—Patient is unable to move right leg which is immobilized with sand-bags.

Reflexes.—Biceps, equal and active on two sides. Patellar and plantar reflexes active in left leg.

Genitalia.—Negative to external examination.

Impression:

Pathologic fracture of right femur of undetermined etiology.

During the patient's stay in the hospital the temperature, pulse and respiration were normal. The blood pressure was within normal limits. The urine showed a few leukocytes, but was otherwise negative. The blood count was as follows: red cells 4,350,000, white cells 10,200, hemoglobin 78. Blood Wassermann and Kahn negative.

Many consultants, including Drs. A. R. Elliott, L. E. Schmidt, and E. W. Ryerson, examined the patient and the x-ray films and all agreed the lesions were difficult to classify, but thought the femoral lesion looked cystic.

During his first stay in the hospital a swelling developed in the region of the seventh rib, anterior axillary line. This lesion has progressed and has never been irradiated.

Following consultation, roentgen therapy was advised, which was given later in the report.

The patient was again hospitalized on November 17, 1931, for further roentgen therapy. He was irradiated and dis-

At present he has very little pain except over the anterior tibial surface which is present only after he goes to bed.

Past Medical History:

Influenza 1917, fairly severe.

Mumps.

No other childhood diseases.

No other illnesses except for arthritis and fracture of femur as outlined in present illness.

Systems:

Head: Some occasional headaches when constipated.

Ears: No earache or discharge. Hearing normal.

Nose: No discharge or obstruction.

Mouth: Most of teeth removed about one year ago because of arthritis. Remaining teeth in poor condition.

No sore throats.

Cardiorespiratory.—No dyspnea, palpitation or chest pain. No history of rheumatic disease or definite cardiac disease. No dependent edema.

Gastro-intestinal.—Appetite very good. No tendency to gastro-intestinal upsets. Bowels regular and only occasionally requiring cathartic. No bloody or tarry stools.

Genito-urinary.—No hematuria, burning or dysuria. Nocturia (1) or (2). Urinates without difficulty. Gonorrhea nine years ago; syphilis denied.

Neuromuscular.—Walks well after dark; no dizziness.

Family History:

Married twenty-six years.

Two pregnancies—first, normal child; second, stillbirth seven months.

Divorced from wife ten years ago.

Social History:

Gateman at LaSalle Street Station, eleven years.

Physical Examination:

Patient has general appearance of a man about fifty years old in excellent health, who appears to be very comfortable.

and there has been a loss in weight of about 20 pounds during the last month.

Dr. A. R. Elliott examined the patient and found considerable fluid in his left chest.

The mass in the right lower anterior axillary line has greatly increased since the last examination. The heart tones are weak, but otherwise normal. No masses or fluid were present in the abdomen.

On January 18, 1934, Dr. T. L. Hansen did a biopsy, removing several large masses from the left humerus. The bone lesion was very vascular and very soft. The humerus was opened along the outer surface and there was practically no bone remaining. The tumor extended well outward into the soft tissues. Bone could be felt along the internal surface of the humerus. When the masses of tissues were cut, areas which looked like tumors were seen. The sections were sent to our pathologist, Dr. Edwin Hirsch, who called the tumor a myeloma without plasma cells.

Roentgen Findings.—The patient was brought to the roentgen department on October 7, 1931, for films of the proximal portion of the right femur. The films showed a large rather circumscribed area cystic in appearance, accompanied by a pathologic fracture, at the level of the lesser trochanter. The line of fracture extended upward and outward through the rarefied area. The fragments were in excellent apposition. We were of the opinion the rarefied area was due to a large cyst. The cortex was thinned but intact and the lesion was quite sharply circumscribed. Believing that the lesion was rather unusual, we examined other bones of the body including the pelvis, lumbar spine, chest, skull and the opposite femur.

The x-ray findings in the other bones examined showed nothing of importance. The chest examination revealed no pathologic changes in the lungs or ribs.

On October 10, 1931, further x-ray studies were made of the proximal third of the right femur. The femur was examined from all possible angles and in one of the films we thought invasion of the cortex could be established. With this

charged on November 21, 1931. His blood and urine were essentially the same as previously. The blood chemistry was as follows:

	Mgm.
Urea.....	9.3
Nonprotein nitrogen.....	30.0
Uric acid.....	4.6
Sugar.....	94.0
Calcium.....	9.7
Inorganic phosphorus.....	3.2
Alkali reserve.....	39.4

The inorganic phosphorus in the urine 0.46 Gm., urea 0.790 (2300 cc. twenty-four hours).

On February 17, 1932, Dr. George W. Hall examined the patient from a neurological standpoint and found nothing abnormal. At his suggestion a spinal puncture was done. The pressure was 450 mm. H 20, in the sitting position; 10 cc. of clear fluid were removed and sent to the laboratory. The Wassermann and Kahn were negative, 1 cell per cmm. Ross Jones faintly positive. Pandy faintly positive.

Numerous blood counts have been made while the patient was being irradiated and the blood has remained within normal limits. We saw the patient in January, 1933, at which time he had a large mass involving his lower right jaw. We did not admit him to the hospital on this occasion, giving him irradiation as an outside patient.

When the patient came into the hospital on January 10, 1934, his jaw had been as he stated "restored to normal and is perfectly well." Pain and swelling in his left arm brought him to the hospital at this time. The urine was negative for albumin, sugar, casts, etc., urinary calcium .041 Gm., phosphorus 0.337 Gm. The blood count had decreased since the last examination, red cells 2,050,000, white cells 6100, hemoglobin 38 per cent. Blood chemistry—urea 12 mgm., nonprotein nitrogen 30 mgm., uric acid 4 mgm., inorganic phosphorus 0.37 mgm., calcium 10.33 mgm. The urine was negative for Bence-Jones bodies.

Physical Examination.—The patient has definitely lost ground since we last saw him. His expression has changed

as given through 1 mm. of copper plus 1 mm. of aluminum. The last treatment was given on November 21, 1931.

The x-ray films taken two months after the treatments showed no further progress of the disease. The texture of the bone improved but did not regenerate. The pain was definitely controlled.

Over a period of two years there has been no evidence of any union of the fracture. The ends of the fragments are



Fig. 267.—Roentgenogram made October 15, 1931, showing the large destructive area accompanied by displacement of the distal fragment.

thickened and smooth, and the medullary cavity appears closed. A study of the most recent films taken January 12, 1934, does not lead one to believe the condition has entirely cleared up. One can believe, however, that the lesion has not progressed, as the cystic area is much smaller and small islands of new bone can be outlined.

in mind, the possibility of a malignant tumor was considered. We were unable to say whether it was primary or secondary.

During the time we were trying to arrive at a diagnosis, the work of Ballin and Morse was in our mind and possibly we were trying too hard to place this patient in the parathyroid group. The blood chemistry which is reported did not bear



Fig. 266.—Roentgenogram made October 9, 1931, showing a large destructive area in proximal third of right femur, accompanied by a pathologic fracture.

out such a diagnosis, although I know Dr. Ballin says there is not always an elevation of the blood calcium in hyperparathyroidism with bone changes.

The patient was treated by high voltage roentgen therapy starting October 12, 1931, a total of ten treatments were given over the lesions in the right femur, using three portals of entry (anterior, posterior and lateral). A grand total of 2185 r



Fig. 269.—Roentgenogram of the pelvis made on January 10, 1934, showing no evidence of pathology involving the bones of the pelvis.



Fig. 270.—Roentgenogram made January 8, 1933, showing large destructive area of lower jaw on right side with incision of the superior cortex accompanied by pathologic fracture.

A biopsy was made by Dr. Plummer on February 4, 1932. A large block of bone was removed from the upper third of the right femur through the greater trochanter. Aseptic necrosis of the proximal third of the right femur.

The pathologic report on the biopsy is as follows:

This piece of bone from the greater trochanter of the right femur is 4 by 3 by 2 cm. thick. The cortex is curved convexly



Fig. 268.—Roentgenogram made June 28, 1932, showing condition of proximal one third of right femur after roentgen therapy.

and rough with adherent muscular and fibrous tissue. The bone has been cut to a depth of 2 cm. The cortex is thin but hard with calcium and the spongy bone beneath is coarsely porous and has wide marrow spaces filled with fat tissue. The bone trabeculae are small and on the surfaces where they are cut, they are like sharp spines and hard. The marrow spaces do not contain a white or gray tumor-like tissue.

Histology.—The histologic preparations are made from the periphery toward the center of a wedge of bone excised from the trochanter of the femur. The cortex is narrow and the bone trabeculae extending from the cortex also are narrow. Their osteogenic membranes are present in but a variable degree. Some of the bone trabeculae are narrow and have lost their osteogenic membranes or this is still present as a narrow layer of atrophic cells. The marrow spaces are wide and are filled with fatty areolar tissue and edematous fibrous tissue. There are only a few marrow spaces with masses of hematopoietic cells.

We did not see the patient again until January 2, 1933, when he returned to the department complaining of a large mass involving the lower right jaw. The mass was as large as a man's fist and was very hard. On palpation it appeared to be a part of the lower jaw. The x-ray films showed a large homogenous rarefied area extending well anterior to the angle. The cortex along the inferior surface was intact, except for a pathologic fracture with no displacement of the fragments.

From the x-ray findings I was of the opinion the lesion was due to a cyst or a large adamantine epithelioma.

The lesion in the jaw presented one rather puzzling area along the alveolar border. At this point the cortex was absent, and this made us suspicious of a malignant tumor. Other bones were again radiographed including femora, skull, pelvis, spine, ribs and chest. No important changes were identified, except for a small rarefied area accompanied by a mass in the seventh rib on the right side.

On January 10, 1933, were irradiated the lower jaw and cervical region, using 200 KVP with $\frac{1}{2}$ mm. copper plus 3 mm. aluminum. A total of four treatments were given at monthly intervals. A total of 800 r given. The mass became smaller two weeks after the treatment and the pain rapidly subsided. On May 17, 1933, no mass could be palpated externally, and the jaw looked normal.

x-Ray films of the jaw as taken on January 12, 1934, show definite evidence of regeneration of bone. The cystic area is



Fig. 271.—Roentgenogram made January 10, 1934, showing a large destructive lesion involving the left humerus.



Fig. 272.—Roentgenogram made January 11, 1934, showing regeneration of bone in right jaw following roentgen therapy.

further study and a biopsy. The patient was very hesitant about having a biopsy as he stated he had practically no pain and the tumor was very much smaller. Physical examination substantiated his statement, the tumor was about one half its original size.

On January 10, 1934, we radiographed the skull, pelvis, femora, spine, chest, tibiae, ulnae as in previous examination no changes were detected in the skull, pelvis or spine. The tibiae, ulnae, radii, and the right humerus showed no evidence of pathology. The chest examination at this time revealed fluid in the lower left chest, and there appears to be definite thickening of the lower left lobe. The seventh rib on the right side showed an area of bone destruction accompanied by a large, hard palpable mass much larger than in January, 1933. Although there is some fluid in the left chest, the patient did not complain of any symptoms.

Conclusions.—It is very difficult to say definitely from the x-ray films what the nature of the pathology is.

First, metastatic malignancy. It seems rather doubtful that a malignancy would continue for such a long period without causing more general changes in the patient. We know the process has been going on for at least two and one-half years, and the probabilities are, it has been present much longer. The fact that the patient has lung pathology at this time might lead one to believe there is a bronchogenic carcinoma which has been present all this time and has caused bone metastasis, but no chest symptoms. It hardly seems possible, however, that a patient would remain alive for so long a period with a carcinoma of the lung; furthermore, he has retained his normal weight until the last month. Frequent chest examinations have revealed no evidence of lung pathology prior to January 12, 1934. I am aware that a small bronchogenic carcinoma may be present and give no x-ray findings.

About a year ago we had a patient referred to us for observation and examination, with a cervical spine lesion, quite typical of malignancy. The patient expired recently, and upon autopsy a small bronchogenic carcinoma of the lung was found.

practically obliterated and the cortex is intact. The alveolar cortex has entirely regenerated. The line of fracture can still be outlined and there is very little evidence of osseous union. The patient can use his jaw as well as ever, and he says it is entirely well. On physical examination there is no swelling present, and the jaw seems solid and functions normally.

The patient returned to the department on January 12, 1934, not because of the jaw or femur, but due to a large swelling of the upper half of the left arm. The arm was about two times its normal size and was hard on palpation. There was no redness or local heat. Great pain was present in the left elbow, probably due to pressure.

The x-ray films of the left humerus showed a large destructive area which apparently is central in origin and has extended through the cortex, periosteum and into the surrounding soft tissues. There are areas of dead bone in the mass, especially along the internal surface. The lesion differs considerably from those present in the jaw and femur, inasmuch as it is not sharply defined but seems to invade and extend irregularly upward and downward. There is no sharp line of demarcation between normal and pathologic tissues, although the cortex along the internal surface of the humerus is very thin and expanded I believe it can still be detected. The greater portion of the mass is made up of a soft substance nonopaque to the x-rays, either tumor tissue—cystic or cartilage. I admit I am at a loss to definitely classify the lesion, and others with whom I have gone over the material are hesitant about making a definite diagnosis. If I were to look at the film of the humerus, not knowing about the other lesion, I would be inclined to say it was a malignant tumor.

Another interesting point in the case is the prompt response of the humeral lesion to deep roentgen therapy. On January 10, 1934, using 200 KVP, $\frac{1}{2}$ mm. copper plus 3 mm. of aluminum, I gave the patient 320 r over the anterior surface of the tumor, and on January 11, 1934, 280 r over the posterior surface of the tumor.

On January 17, 1934, I had him return to the hospital for

it is impossible to classify tumors as to their histology from x-ray findings and I am just as firm in my belief that it is not necessary to try. If we can determine whether or not a bone lesion is malignant or benign, we are doing all that can be expected of us. Even to do this in all cases is asking and expecting a great deal.

This case also demonstrates how difficult it is to definitely classify these bone lesions even from the microscopical sections. The first sections taken from the femur showed changes said to be an aseptic necrosis, whereas the sections taken from the humerus showed changes classified as myeloma.

It is evident that a patient may live for a long period with carcinoma of the lung and have no symptoms or findings referable to the chest.

We had for some time considered the possibility of the lesions being due to a hyperparathyroidism, but I believe this can be ruled out, especially as we view the lesion of the humerus and also the absence of any change in the blood calcium militates against this diagnosis.

Primary sarcoma osteogenic with metastasis must also be considered. The lesion in the femur and the jaw were not typical of a malignant tumor but did show areas of invasion which could well be interpreted as malignant tumors.

The therapeutic test using irradiation may be of some value in arriving at a diagnosis. The fact that two of the lesions, jaw and humerus, responded promptly to the rays, and the lesion in the femur was at least held in control makes one think of the possibility of the tumor being of the myeloma group.

We have known for years that certain types of myelomata respond to irradiation although I have never experienced such prompt and lasting benefit when treating multiple myeloma. In one patient we treated some years ago for a single myeloma of the ilium, the results were satisfactory, but the response not nearly so rapid.

The endothelial myeloma type of tumor usually responds very promptly to irradiation but the results are as a rule not so lasting.

From the data we have obtained, clinical and radiological, I believe we are justified in saying the bone lesions are probably due to a malignant tumor which responds to irradiation. It would be difficult for me to classify the lesions as multiple myeloma from the x-ray findings alone as every case of multiple myeloma I have seen has shown more involvement of the flat bones, such as the ribs, skull, pelvis, scapula, vertebrae. I have seen patients before with involvement of the humerus, but they always were accompanied by extensive lesions in the flat bones and spine.

I believe this case teaches us one very important lesson that

She was admitted to the hospital October 8, 1933. She stated that while at work in a cleaning establishment two years ago, she noticed blood in her urine; she suffered no pain at that time and there was no frequency or dysuria. Her urine would appear grossly normal for two or three days and then suddenly become bloody. About one month after the initial hematuria, she began to have pain in the left lumbar area; she would be seized with short attacks of severe colicky pain which would radiate to the epigastrium. In the last few months there has been pain in the right lower quadrant. There has been no frequency or dysuria at any time. She has an occasional headache. There has been a loss of 21 pounds in weight in the past eighteen months. She has never had chills, fever or sweats. Her menstrual history is entirely normal.

The patient had scarlet fever and measles as a child; there were no complications. Her tonsils were removed at the age of twelve. Her family history is without significance; there are no hereditary diseases in the family. She is married; her husband and two children are living and healthy.

Physical examination revealed a thin, sallow, white adult female, lying quietly in bed. Her pulse was 74, temperature 98.4° F., respirations 18, and blood pressure 102/68. The eye-grounds and reflexes were normal. There was moderate dental caries. There was some increased dulness over the left posterior chest up to the level of the third and fourth thoracic vertebrae; voice and breath sounds decreased over this area also. The abdomen was flat and showed no scars, masses, tenderness or rigidity. The lower edge of the right kidney could be felt by bimanual palpation. All superficial reflexes were normal.

On admission the urine was straw color, alkaline in reaction and hazy; the specific gravity was 1.012; it contained 40 mg. of albumin per 100 cc.; there was no sugar or casts; there were 30 to 50 erythrocytes and 15 to 25 leukocytes to the high power microscopical field; no bacteria were seen. Blood studies showed 3,740,000 erythrocytes per cmm., 7950 leukocytes per cmm., and 71 per cent hemoglobin. The blood Wassermann and Kahn reactions were negative. Chemical ex-

CLINIC OF DR. HARRY CULVER AND DR. WILLIAM J. BAKER

ST. LUKE'S HOSPITAL

UNILATERAL HYDRO-URETERONEPHROSIS WITHOUT EVIDENCE OF OBSTRUCTION

It is unusual to find a large unilateral hydro-ureter and hydronephrosis in an adult with no obstruction to the bladder outlet and with normal appearing ureteral orifices; such findings are more unique in the absence of infection or any obstruction in the removed ureter and kidney. We wish to present such a case.

Mrs. M. S., white, aged twenty-nine, and a housewife, came to St. Luke's Hospital Out-patient Department, September 25, 1933. She complained that she had been passing bloody urine periodically for over two years and had noticed a left lumbar pain during all that time. Because she had been using benzidine in a cleaning establishment, her family doctor had believed she was suffering from a chemical hematuria.

Physical examination revealed a tall, very lean, fever-free female; there were no palpable abdominal masses or tender areas. Observation cystoscopy revealed bloody urine, a normal-looking bladder mucosa, and a good capacity bladder with normal-appearing ureteral orifices. No. 6 F. ureteral catheters passed unobstructed up both ureters; the drainage from the right side was a normal amber urine; that from the left side was a very dilute, fast-dripping, pale urine. Intravenous phenol-sulphonaphthalein appeared from the right side in very good concentration in six minutes; no dye appeared from the left side after waiting thirty minutes. In view of these findings on cursory examination, the patient was advised to enter the hospital for further diagnostic procedures and care.

region. The left catheter was withdrawn so that but 3 cm. remained in the ureter and the patient placed in the Trendelenburg position as 100 cc. of Cunningham's solution were slowly injected without pain or distress, and the film repeated. Again the pyelographic fluid has essentially remained in the lower fourth of a much dilated ureter, with no regurgitation of the fluid into the bladder.

Intravenous urography showed that there was a very large left hydro-ureter and hydronephrosis. The function of the right kidney was within normal limits; in five minutes the dye could be definitely outlined. There was some delay in the function of the left kidney; at the end of thirty minutes the opaque solution could be outlined, denoting that there was still some function.

Laboratory study of the urine specimens which were collected at cystoscopy revealed the bladder urine to contain a great deal of cellular debris, a few erythrocytes, leukocytes and epithelial cells and no organisms; no acid-fast bacilli were seen and the cultures were sterile after forty-eight hours. Urine from the right kidney contained an occasional epithelial cell, a small amount of amorphous material, and no bacteria; no acid-fast bacilli were seen and the cultures were sterile after forty-eight hours. Urine from the left kidney contained many erythrocytes, frequent leukocytes, much debris, and no organisms; no acid-fast bacilli were seen and the cultures were sterile after forty-eight hours.

On the basis of the above studies, a preoperative diagnosis of chronic hydro-ureter and hydronephrosis was made and left ureteronephrectomy was recommended.

Operation.—Under ether anesthesia the usual curved kidney incision was used and extended downward sufficiently to do a complete nephro-ureterectomy with one incision. Adequate kidney exposure was made with ease as there were no adhesions and the perirenal fat stripped from the kidney readily. It was then seen that we were dealing with a large flabby hydronephrotic sac and hydro-ureter as large as the normal small intestine. The renal pedicle was readily isolated and clamped, doubly tied

amination of the blood showed 13.1 mg. of urea nitrogen per 100 cc. of blood; 33.3 mg. of total nonprotein nitrogen per 100 cc. of blood, and 129 mg. of sugar per 100 cc. of blood. The two-hour intravenous phenolphthalein kidney function test returned 20 per cent of the dye in the first hour and 15 per cent in the second hour.

Roentgen-ray study of the chest showed the upper right chest to be retracted. The diaphragm is regular on both sides. The costophrenic angles are clear. The root shadows are moderately increased, and extend down into both lower lobes, especially the right. There is no evidence of recent pathology in either lung which might be due to an active tuberculosis.

Cystoscopy was performed on October 9, 1933. A No. 24 F. cystoscope was passed without obstruction and 4 ounces of smoky, turbid urine was collected from the bladder. The bladder tolerance and capacity were very good. Both ureteral orifices were normally shaped and placed. No. 5 F. shadow casting catheters were readily passed up both ureters; there was a normal flow of amber urine from the right side and a fast flow of dilute pale urine from the left side. Intravenous phenolsulphonephthalein appeared on the right side in three minutes in excellent concentration; no dye appeared on the left side after waiting twenty-three minutes. An x-ray picture was taken of the kidneys, ureters and bladder with the catheters in situ. After pulling the left catheter down about 5 cm., 25 cc. of Cunningham's solution were injected into this ureter without any indication of pain and a roentgenogram made. This solution was allowed to drain from the left side before injecting 7 cc. of Cunningham's solution into the right kidney and ureter; a roentgenogram was taken of the right side.

When an attempt was made to interpret the above films, a normal right pyelo-ureterogram was seen. The left ureteral catheter was coiled up just outside of the bladder. On close inspection, an irregular wide column shadow could be seen, which was dense, had smooth borders and tortuous for a distance of 4 or 5 inches adjacent to the bladder, above which an indistinct shadow of similar dimensions continued to the kidney

was a marked widening of the renal pelvis and a dilatation of the major and minor calyces. The whole kidney structure was like a bag (Fig. 273). The functional tissues ranged between 5 and 8 mm. in thickness. The lining surface was finely mammillated. The markedly thickened wall of the ureter ranged between 3 and 5 mm. A small segment of ureter and a piece of kidney tissue were taken for histologic examination.

Histologically, the width of the parenchyma tissue, including both the cortex and medulla was diminished to about 6 mm. The cortex exceeded slightly the medulla. The tubules had the usual lining cells. Focally, there were a few hyalinized glomeruli and small scars. There were slight inflammatory changes along the pelvic margin in aggregates of round cells like lymphocytes and some plasma cells. The blood vessels had thick muscular and hyaline fibrous walls. The ureter had a thick wall. The muscle portions had markedly hypertrophied cells and between these bundles there was an excessive growth of fibrous tissue, some of which were edematous. Along the lining edge in the submucosa were collections of round cells. A final diagnosis of marked left hydro-ureter and hydronephrosis was made.

The patient made an uneventful recovery and was discharged to the out-patient department on the fourteenth post-operative day. One week later, voided urine was clear and a sediment revealed an occasional pus cell; there was no residual bladder urine. One month after her operation she was discharged from the out-patient department as cured.

The etiology of so-called "idiopathic hydro-ureter" and "hydronephrosis" is entirely speculative. It is a well-known fact that ureters in fetuses up to the fourth or fifth month are of enormous caliber as compared with the size of the kidney and the rest of the body; it might be supposed that the ureter instead of diminishing in caliber from this period as is normal, could continue to develop concurrently with the rest of the body and remain even in adult life as voluminous in caliber. Hinman¹ refers to this as the persistence of the sausage type of fetal ureter.

and cut. The ureter was easily isolated down to the bladder, at which point its caliber was narrowed but apparently not strictured; it was doubly ligated and cut close to the bladder between the ligatures, thus removing the entire kidney and ureter unopened *en masse*. All spaces were adequately drained and the wound closed in the usual way in layers.

Pathology.—A study of the removed kidney and ureter showed the left kidney was 16.5 cm. long, 8 cm. wide, and in its

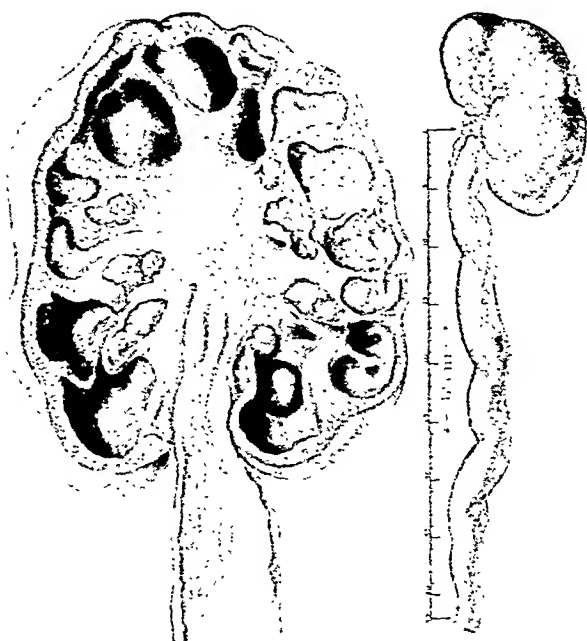


Fig. 273.—Drawing actual size of kidney and upper ureter. Reduced to represent entire specimen.

collapsed state 3.5 cm. thick. It was fluctuant like a partly inflated bag. Continuous below was hugely distended ureter which was 42 cm. long. It was markedly tortuous and thick-walled. At the bladder end the outside diameter was as much as 3 cm. Just below the ureteropelvic junction it was 1.5 cm. The blood vessels had been cut off close to the hilum of the kidney. When the kidney was split along its convex edge, there

which may not now be evident but which must have been evident at some previous time.

Pathologic and histologic findings suggest that obstruction of some sort at the ureterovesical junction or in the intramural ureter was primarily the cause for the lesion here described. Inasmuch as this was a clinical and not an autopsy study, no known means are available to determine the possibility of a mucosal valve in this area, while it was very definitely established that there was no appreciable stenosis from below upward. It is held that chronic, but perhaps intermittent spasm of the ureterovesical musculature must in some instances be a primary cause of this condition, but logically could not be seriously considered in an unilateral case, nor could any such a generalized condition as toxic effects on the ureteral musculature.

Segmental atony may reasonably be considered as a factor in ureteral dilatation as may congenital hyperplasia, but since the ureteral musculature of the greatly dilated ureter just above the bladder showed marked hypertrophy of its fibers, these considerations can be dismissed.

Hypoesthesia and hyperesthesia of the ureteral mucosa are interesting conjectures as a cause of ureteral dilatation and cannot be ruled out here in spite of the unilaterality of the lesion.

With nothing more than a fairly accurate clinical study and due consideration of all available known causes of ureteral dilatation to direct us in our conclusions, we are of the opinion that a mucosal valve at the uterovesical junction or in the intramural ureter best explains the pathologic process produced.

This lesion will be recorded as one of sterile hydro-ureteronephrosis of undetermined cause until further pertinent findings are available.

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Again it can be supposed that there has been previous obstruction by fetal valves which have undergone regression but have left a dilated ureter and kidney.

Experimental evidence is lacking to prove the part which mucosal hypoaesthesia or hyperaesthesia may play in these dilatations. It is reasonable to believe that there may have been an early primary hypoplasia of muscle to allow later dilatation.

Hepburn² and others believe that spasm of the ureterovesical junction may play a part in these dilatations. His theory fits bilateral conditions but does not logically apply to our case.

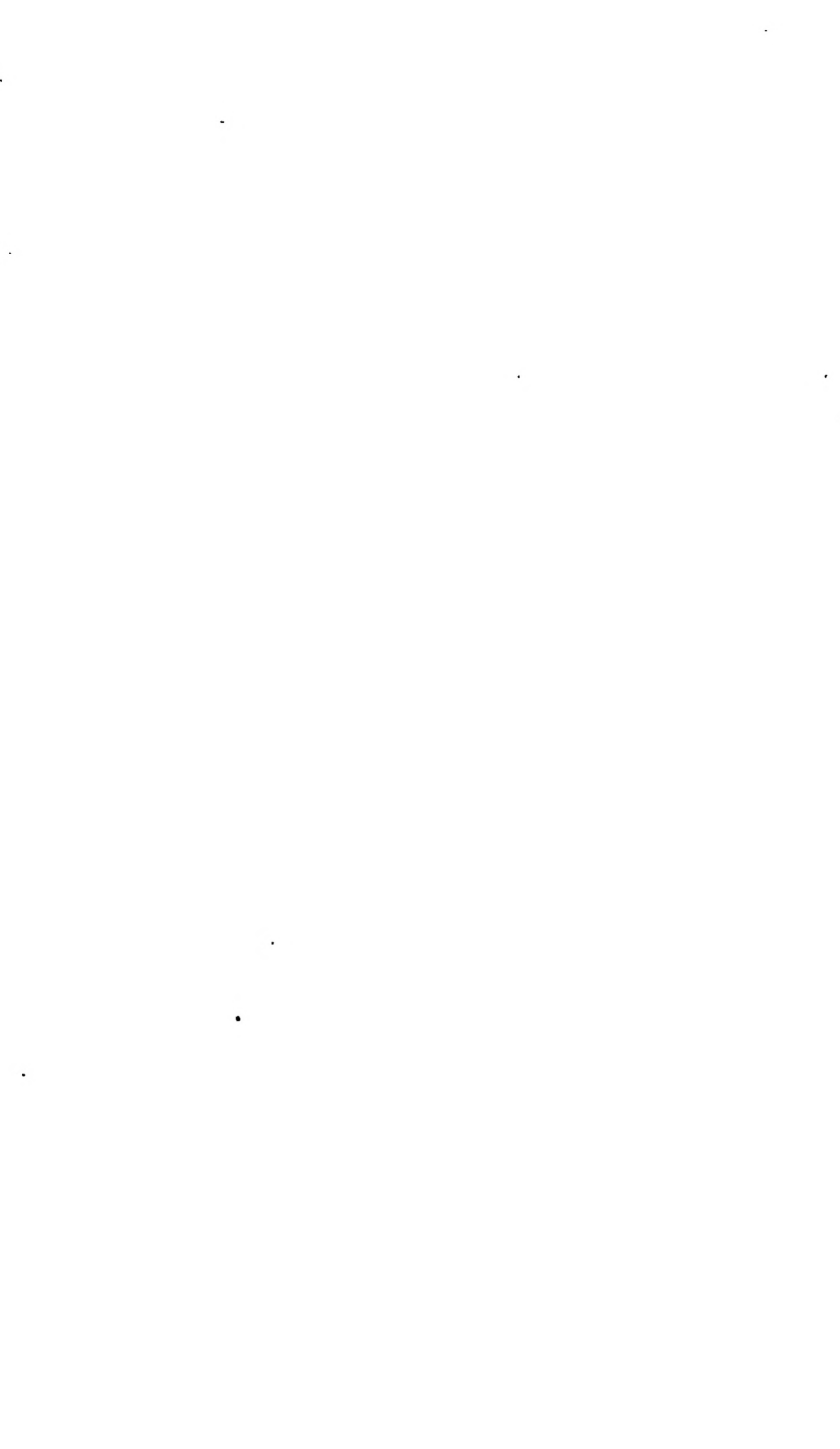
Braasch³ has argued that many of the urinary tract dilatations are the result of inflammatory processes. Whether the dilatation or inflammation is primary, is not always easily decided. Our case was not infected at the time of this study, but the histologic study revealed marked fibrosis as well as groups of round and plasma cells consistent with a controlled and healing inflammatory process, which obviously must be of the metastatic type.

Beach⁴ believes that denervation of the ureter is always followed by dilatation. Hinman¹ was unable to obtain hydronephrosis by denervating the kidney. It is true that the uterovesical junction of our case seemed perfectly competent and did not permit regurgitation into the bladder. A pertinent procedure was neglected; although the ureteral orifice appeared normal it would have been interesting and valuable to see what a cystogram would show. The findings quite definitely indicated the competency of the ureterovesical valve as far as control from above downward was concerned, but this is not evidence that reflux was not present.

Long standing, slowly developing spasmodic contraction of the bladder will cause upper urinary tract dilatation. Our patient had a normal bladder.

Some workers have believed that ureteral and kidney stasis can be caused by toxins.

It seems to us that unilateral hydro-ureter and hydronephrosis are probably always primarily caused by obstruction



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I use the term acute diffuse spondylitis to infer an acute primary infectious process involving the lateral articulations. These are the only true joints in the spinal column. In our experience this disease is rare. The thing that interests us so much is whether it is an early manifestation of spondylitis ankylopoietica or whether it is possible to have an inflammatory process in these articulations which can clear up entirely. Theoretically this seems possible. Clinically, we have an acute rheumatic fever with exquisitely tender joints. These clear up, as a rule, and leave no trace of joint deformity. On the other hand, we have an acute onset of rheumatoid arthritis which may result in more or less permanent deformity of the joints. In the former case the pathologic process apparently is confined to a synovitis or hyperemia of the synovial membrane, while in the later case the process goes on to a pannus formation over the articular surface and a destruction of the cartilage. Later on ankylosis may occur. It is of course too early at present to tell what course the case being presented will follow. x-Rays are of little value early in differentiating these two types of spinal conditions for the pathologic changes visible on the x-ray films may not show for one or more years in the spondylitis ankylopoietica. As you look at the patient today, it is hard to realize that a few weeks ago even the slightest pressure over the spine was intolerable. The process seems to be clearing up and I would like to feel that there will be no permanent damage to the lateral articulations. If this is true, I cannot see why the joints might not become normal again, as is the case in acute rheumatic fever. If there is no permanent damage then there should be no stiffness of the spine in later years.

The history and the pertinent physical findings as they have occurred are as follows: The patient is a student nurse, twenty-three years of age. She has been under our medical supervision and care for three years. Two and one-half years ago she developed acute arthritis involving the ankles, knees, shoulders and hips. Pain persisted in these joints for two or three months, following which the joints cleared up and there has remained no permanent joint pathology. She then spent

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ACUTE DIFFUSE SPONDYLITIS

THERE are two types of chronic arthritis of the spine, osteoarthrosis and rheumatoid arthritis. Osteoarthrosis is now being looked upon as a noninfectious process which probably is the result of trauma to the vertebrae after the intervertebral disks have become injured or have ceased to function. As the result of this trauma, osteophytes develop on the articulating surfaces of the vertebrae and often involve the exit of the spinal nerves. Almost 100 per cent of people past sixty years of age show osteoarthrosis of the spine. Rheumatoid arthritis of the spine is confined to the lateral articulations (facets) early in the course of the disease. Apparently the first pathologic process is a synovitis. Later there develops an ankylosis of these joints, a calcification of the anterior longitudinal ligaments and finally an osteoporosis of the bodies of the vertebrae which may extend even through the intervertebral disks. The final picture is a spondylitis ankylopoietica which on x-ray has a characteristic bamboo-like appearance. Of course, this process can terminate at any one of the above-named stages.

It is not hard to see how acute exacerbations might occur in the course of these two types of chronic disease which usually take a great many years to fully develop. As an example of an acute exacerbation of osteoarthrosis an acute lumbago might be the result of trauma affecting the spinal nerves by pressure of osteophytes surrounding the exit of the nerves. The pain could be very severe and might suggest some acute infectious process, which of course it would not be in this case. An acute exacerbation is started in a rheumatoid arthritis of the spine whenever there is an extension or recurrence of the infectious process.

symptoms complained of could be explained by a radicular involvement. There was a band of hyperesthesia corresponding to the eighth and ninth dorsal nerves, but otherwise the neurological examination was negative.

Because of the acute symptoms it was decided to try some foreign protein therapy to see if the infectious process could be aborted. Ten million mixed typhoid bacilli were given intravenously on November 24th. The patient had no chill following this vaccine but developed a maximum temperature of 100° F. two and one-half hours later. With the increase in temperature the pain over the arms and legs and about the thorax became unbearable. Even respiration caused tremendous intercostal pain. The patient became hysterical and morphine was needed to quiet her. On awakening from the hypnotic, she complained of inability to use the left arm, and of some decrease in strength in the right. Examination revealed both subjective numbness as well as objective hypesthesia involving the left hand and forearm, more on the median side. There was practically no strength in the left hand and diminished strength in the right hand. There was hypesthesia over the left deltoid region and even over the distribution of the great occipital nerves. It was difficult to explain the increase in radicular involvement on the basis of the reaction set up by the typhoid vaccine. The patient's condition had been about stationary for forty-eight hours previous to the injection and I do not believe the picture presented was the normal sequence of events. It is my belief that the increased damage was due to trauma to the spinal nerves which resulted from the hysteria of the patient following the increase in pain after the administration of the typhoid vaccine. The patient was confined to bed until December 26th and we believe this was the most important part of the treatment, for it decreased to a minimum the trauma to the spinal nerves. The pain gradually subsided and the strength in the muscles of the arms and hands increased.

The temperature was intermittently as high as 99.6° F. until December 10th and has since been normal. The white blood count was over 12,750 until December 13th, when it was re-

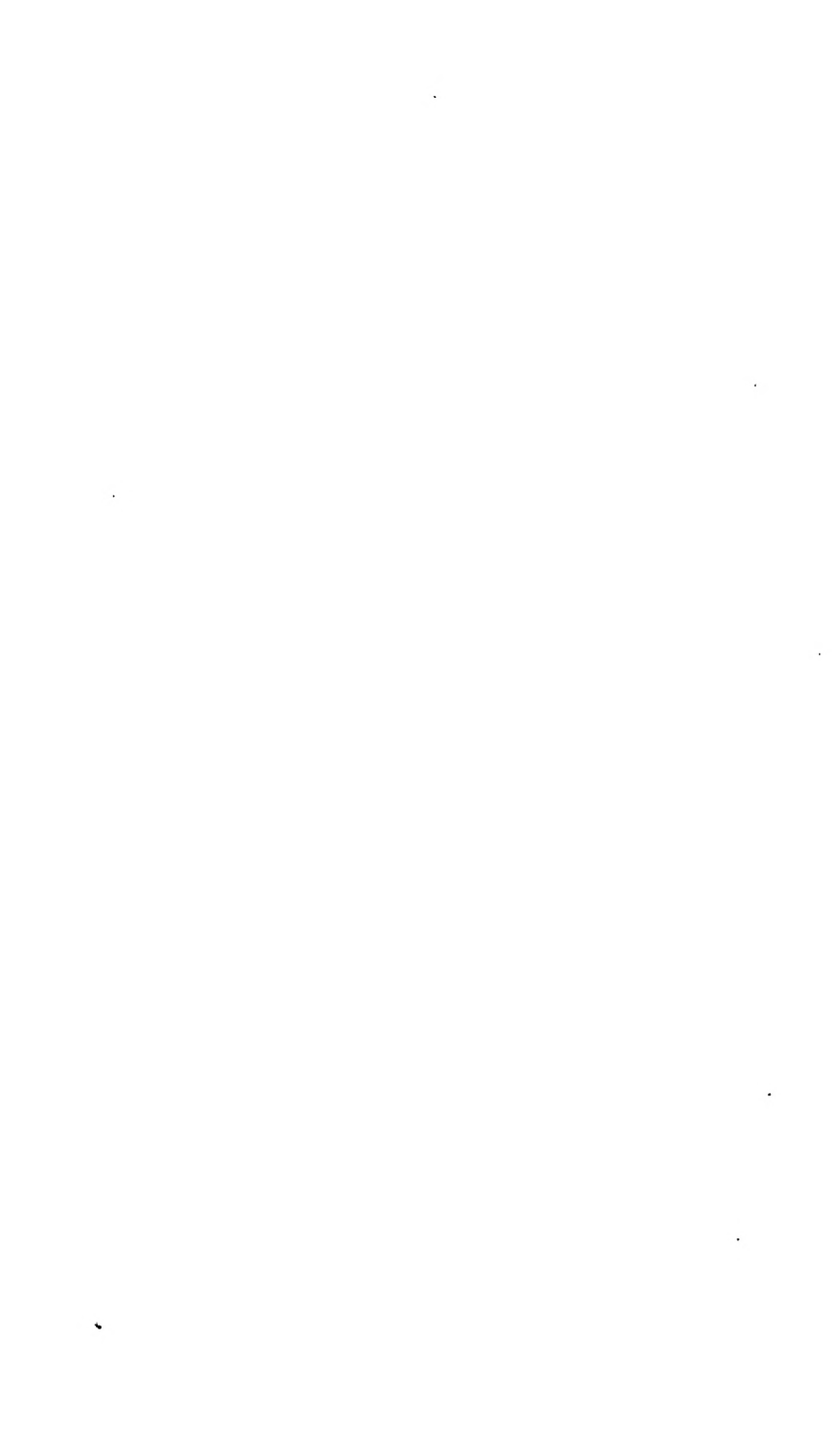
one year resting and returned to continue her training in September, 1932. There has been no past history of lumbago, sciatica or neuritis, and there is no history at the present time of acute trauma to the back.

I first saw the patient November 17, 1933. She complained of a stiff neck of two to three days' duration and tinnitus. She had had a head cold of moderate severity two weeks before, but this had entirely cleared up. There had been some headache but on close questioning, the headache seemed to be a pain over the occiput and vertex which was aggravated by moving the head. The pain described covered the area supplied by the great occipital nerves. In addition to this, movement of the head caused severe pain in the neck. There was no tenderness over the thoracic or lumbar spine and the patient could bend freely. The ear drums were normal. I felt the patient had an acute cervical neuritis and dismissed her with only symptomatic treatment.

The next day the pain in the neck became so severe that she entered the hospital. By this time there was some tenderness and pain over the upper dorsal region, and it was painful to bend her back or to move in bed. Her temperature was 99.6° F. and the white blood count was 8400. The urine was normal. The blood pressure was 115/65 and the heart and lungs were normal.

In the next twenty-four hours her entire spine was excruciatingly tender. Even the slightest pressure over the spinous processes or over the lateral articulations caused intolerable pain. There was some pain over the shoulders but none down the arms or legs.

On November 22nd, the patient was seen by Dr. Joseph L. Miller. For the first time there was a positive Kernig, especially on the right. We felt this was due to the sciatica the patient now complained of, but a neurologist, Dr. George W. Hall, was called in for his opinion. The temperature elevation was very slight, averaging a maximum of 99.6° to 100° F. daily. White blood count was now 13,900. Dr. Hall felt that there was no central nervous system pathology and that all of the



duced to 9500, and has since been below this. x-Ray examination of the spine December 7th did not give any information. The lateral articulations show very distinctly and appear perfectly normal. When the patient was permitted out of bed on December 26th, five weeks after the onset, she was unable to bear weight on her limbs. Apparently, as in the case of the arm muscles, there was a great diminution of strength. This had not been recognized before. After one week she could take a few steps and today (January 10th) she can walk fairly well. There is still some tenderness over the dorsal and lumbar spine and she cannot bend over very far. Physiotherapy to the point of tolerance has been employed throughout her entire illness.

In summary, I would like to repeat that the patient presents what we believe to be an acute diffuse spondylitis. The process seems to be confined to the lateral articulations, although x-ray evidence is entirely lacking as might be expected. The spinal nerves are involved as they leave the vertebrae either by direct extension of the inflammatory process or by pressure. The only possible etiologic factor known is an acute head cold which developed two weeks before the present illness. The symptoms have practically disappeared except a slight stiffness in the dorsal and lumbar regions, but it is yet too early to tell what the final outcome will be.

NOTE.—The patient was seen March 28th. She had been on a vacation since leaving the hospital. At the present time it is impossible to find any evidence of the illness. She has no muscle weakness in the arms or legs and no pain. She can bend her back the normal range of motion without pain or stiffness and is not restricted in her activities. She is again resuming her duties as a nurse.

Examination of the patient on March 6th showed her to be in good health generally. Her weight was 138 and her height 5 feet, 7½ inches. Her development was entirely symmetrical. Examination of the eyegrounds revealed nothing of interest. All ocular movements were normal and no nystagmus was present. Her face and neck would flush quite easily, revealing a rather sensitive vasomotor control. She talked quite calmly but confessed to being quite nervous, which she said was foreign to her nature up until two years before the date of examination. Her throat revealed fairly large tonsils, which did not appear to be diseased. There appeared to be no enlargement of the thyroid gland. No cervical adenopathy was observed.

Chest examination revealed normally developed breasts with equal chest expansion and no lung pathology. The heart borders were well within normal limits. Her radial pulse was 42 but the apex beat revealed coupling with an apex rate of 84. The tones of the normal beat were perfectly normal. Blood pressure was 132/74. Examination of the abdomen was negative as was examination of the extremities. All reflexes were well within normal limits. No pathologic reflexes were elicited. Pressure over the carotid sinus and exercise did not materially change the heart rate. On inquiry I found that the patient had had the slow pulse for two years and had never during that time found her pulse over 50.

Feeling that the mechanism was a sinus bradycardia due to excess vagal stimulation, I secured a number of electrocardiograms of her mechanism before medication and then injected 1/100 grain of atropine subcutaneously. This produced a somewhat more rapid rate and the coupled beats were not constant. A second 1/100 grain of atropine was given in fifteen minutes and this time the rate went to 90 and was perfectly regular with no extrasystoles. The patient experienced the usual dryness of the mouth and some slight feeling of fulness in the head from the atropine but was otherwise quite delighted to find her heart rate once more as it had been several years before. She returned to her home and a nurse checked her pulse for the balance of that day and the entire day following. There was no

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ANALYSIS OF AN UNUSUAL CASE OF COUPLED VENTRICULAR BEATS

I WISH to present this morning a case that I have found of interest during the past ten months and which to me seems to shed a good deal of light on the mechanism involved in coupled ventricular beats producing in some instances pulsus bigeminus in otherwise healthy adults.

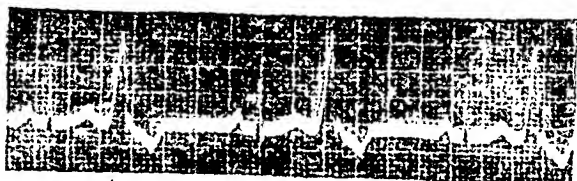
The patient in question was referred to me on March 6, 1933, by Dr. Alphonse McMahon of St. Louis, Missouri. Dr. McMahon had examined the patient during the summer of 1932 and found her with a bigeminal pulse produced by extrasystoles occurring at regular intervals.

The patient was an adult female, aged thirty-eight years, of more than average intelligence. Her chief complaints were headaches, which she described as a dull feeling through the head rather than an actual ache, and nervousness. This was coupled with partial loss of memory for recent events, which she herself analyzed as being due to lack of attention. She also complained of some slight fainting spells in which she would tend to tip to the left side without actually falling. She also felt that she inclined to deviate to the left when walking.

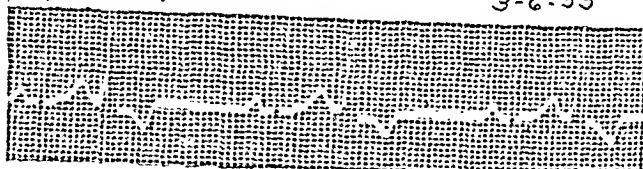
Her past history revealed two pregnancies, with normal deliveries, in 1922 and 1925. She had complained of slight deafness at times, which had become so pronounced in 1927 that she had consulted Dr. R. P. Scholz in St. Louis. Her marital history brought out the fact that she had been having some domestic difficulty and was at the time of my first examination filing divorce papers, charging her husband with drunkenness and neglect.

LEAD II

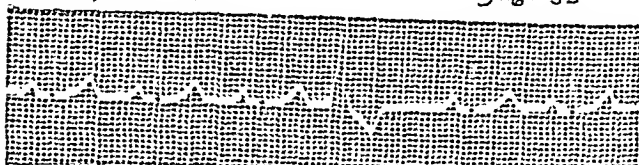
8-12-32

*Before Atropine*

3-6-33

*After 1/100 Atropine*

3-6-33

*After 1/50 Atropine*

3-6-33

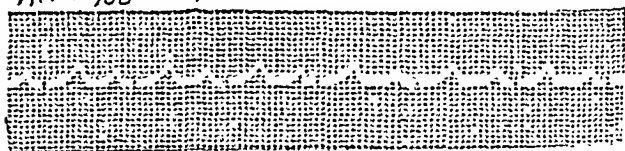


Fig. 274.

have been able to discover, however, has shown this slow rate to extend over as long a period of time nor has there been any

evidence of coupling and the rate remained high until thirty-six hours after the administration of atropine at which time it fell to the low forties once more.

Feeling that there was a possibility of brain tumor in this case, I had the patient examined by Dr. John Favill, who found no neurological abnormality other than in the sense of hearing. Her left ear heard the watch at a distance of 5 inches and the right at 12 inches. Rinné was negative on both sides. There was no evidence of increased intracranial pressure. Her gradual loss of hearing for six years, with a history of tinnitus and buzzing sounds two years ago, inclined him to the belief that her labyrinths were involved, and that some abnormal vagus irritative effect was the result of this. Communication with Dr. Scholz in St. Louis revealed that her examination in 1922 had revealed no vestibular disorder at that time and that her hearing disorder was apparently coming from a mild tubotympanic catarrh. He had treated her several times that summer and local treatment seemed to give her much relief.

The patient was seen again on March 12, 1933, six days after her first electrocardiograms, and appeared to be in a very optimistic frame of mind. She declared that she felt better than she had in two years, part of which she explained by the fact that the day before, her divorce had been granted and she had been given custody of both children. In addition to that, upon awakening that morning she had experienced such a complete sense of relief from her previous depressed feelings in the heart that she was quite pleased to find her pulse beating at a rate of 72. Examination revealed a perfectly normal cardiac mechanism. Her rate in the office was 76 and she had a normal response to exercise. She was put at rest lying down for thirty minutes and at no time did the previous bradycardia reappear. Blood pressure was 120/80. No medication other than the atropine used six days before was given.

Discussion.—This case appears to shed a good deal of light upon the mechanism of some types of bradycardia. It has been observed by a number of authors that the acute melancholias will sometimes produce a true bradycardia. Nothing that

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QUANTITATIVE FEEDING OF PATIENTS AS A DIAGNOSTIC PROCEDURE IN OBSCURE CASES OF HYPERTHYROIDISM

It is the purpose of this clinic to consider the energy requirements of the thyrotoxic patient, and to show how in obscure cases the quantitative feeding of patients may prove a valuable diagnostic procedure.

SOME SOURCES OF ERROR IN METABOLIC RATE ESTIMATIONS

In the basal state, when the machine is idling, we have a "standard" expenditure of energy. This is not the lowest energy expenditure, for lower values are obtained during sleep. It is the lowest value obtainable during the waking hours, when the patient is thoroughly relaxed and free from the stimulation of food. When one asks how this energy is utilized, he is confronted with various answers. In general a 25 per cent expenditure is assigned to the striated muscles. They are the seat of oxidative changes, which may supply energy to other parts of the body. More important, however, is the local expenditure which is concerned in the maintenance of varying degrees of contraction designated "muscle tone." If an inhalation anesthetic is given, the muscle tone is depressed and a state of surgical relaxation obtained. If one wishes a greater depression of tone, a spinal anesthetic is used. If a frog is pithed and the sciatic nerve on one side is cut, the corresponding leg elongates more than the other. If one takes an electrical record of such a contraction, it appears to be tetanic in char-

acter and to depend on the fusion of multiple contractions of the individual motor units. Each motor unit comprises an axone and its accompanying muscle fibers. In reality we are dealing with reflex stimulation of these motor units. The afferent pathways come from a wide variety of receptor surfaces scattered over the entire body. For example muscle tone is an important factor in the body's response to gravity. And so it can be readily seen that the retina, the semicircular canals, and the proprioceptors in the muscles become afferent receptors for these reflexes. Other specific instances might be cited enlarging the receptor field.

It should be obvious, therefore, that it may be difficult and at times impossible to establish "standard" or basal conditions in the muscles. An apprehensive patient may unconsciously bombard antagonistic muscles with extra reflex stimulation in order that movements be abolished and so double the energy expenditure. He will tell you that he is perfectly relaxed, and yet his arms and legs are so stiff that they are moved with difficulty. In other cases more subtle somatic or visceral reflexes which escape detection may be active. Thus a fleeting emotional upset may liberate a discharge of adrenalin, or a wave of nausea may establish widespread circulatory changes. Patients, who cause errors of this kind in the taking of rates, include those with mild anxiety neuroses, those with neurocirculatory asthenia, and those frankly labeled as psychasthenics. Hence, the experienced physician realizes that frequently several metabolic rates must be run before a dependable one is obtained. Physicians with less experience often fall into this pitfall. They have heard that a single metabolic rate is not significant, and yet, since they did not understand the mechanisms of the production of errors, they have forgotten or ignored the advice.

There is a group of patients with Parkinson's syndrome, who offer diagnostic difficulties. Some of these have an associated hyperthyroidism, but by far the larger number do not have hyperthyroidism. Such a patient may have an unobtrusive tremor and beginning muscular rigidity. It is quite

obvious that an elevated rate would result from the changes in the behavior of these muscles and increased energy requirement would be expected.

An orthopneic heart case, who has difficulty in breathing, when lying quietly in bed, could not be expected to fulfill the requirements for an accurate estimation of the basal metabolic rate. Occasionally the physicians who have made a clinical diagnosis of hyperthyroidism on such patients accept an increased metabolic rate obtained on such patients as diagnostic confirmation of their clinical conclusions. It is much safer and more scientific to base one's diagnosis entirely on the clinical evidence.

Cases of essential hypertension give elevated rates of plus 20 per cent to plus 30 per cent. The mechanism of this elevation is not understood. It frequently is misleading and one is sorely taxed to arrive at the truth in these cases.

The true hyperthyroid is an individual who has an increased amount of thyroxin active in his body. This has speeded up the oxidative processes so that an excess quantity of energy has been liberated in the form of heat. Excess heat production is the cardinal symptom. If food is not available for this transformation, then the body structure is attacked, with a resulting weight loss. Thyroxin also perverts the muscular physiology in such a way that fine tremors appear which are intensified by effort. While this tremor is a factor in the increased rate, it is a small one as compared with the acceleration of the oxidative processes.

It is obvious, therefore, that there are many situations in which the metabolic rate estimations may be confusing and misleading. It would be valuable, therefore, to have some objective test yielding similar information to corroborate clinical deductions.

THE ESTIMATION OF METABOLIC RATE BY WEIGHT CHANGES OF PATIENTS WHO ARE EATING QUANTITATIVE DIETS

A patient with a normal metabolic rate under the ambulatory life of the hospital will not lose weight when eating a

30 per cent additional ($178 + (30 \times 178) = 231$ per cent) or 2926 calories. Her diet was 2896, then 2911, and she remained on this until 2/22/23, sixteen days without a gain in weight (weight 2/6/28, $113\frac{1}{2}$ pounds, on 2/22/28 weight 114 pounds).

It is to be noted that there was a gain of weight from 106 pounds on 2/2/28 to $113\frac{1}{2}$ pounds on 2/6/28. Coincident with this gain the calories were increased 741, but the glucose in diet was increased 29.2 Gm. (from 139.8 to 169 Gm.). Both of these may have been factors in enabling the body to retain more water, and so establish a greater degree of hydration.

2/11/28: Lugol's solution started.

2/13/28: Weight 114 pounds.

2/20/28: Weight 114 pounds.

2/22/28: Weight 114 pounds. It was now planned to increase the diet sufficiently to establish a progressive gain in weight. An ambulatory patient under insulin administration should gain weight if his calories are increased to basal plus 50 per cent. As shown above, the evidence favors a true metabolic rate in this patient of 178 per cent. We must, therefore, feed her 50 per cent above this or 267 per cent. Accordingly, a new diet order was filled as follows: carbohydrate 147.9, protein 85.9, fat 283.1, glucose 225, fatty acids 293.8, ratio 1.3, calories 3479. The theoretical amount she should eat was 267 per cent of 1267 calories or 3383 calories.

2/24/28: The effect of Lugol's solution, sedatives, and rest were shown by a lowering of her rate as estimated by oxygen consumption to plus 42 per cent. It was evident, therefore, that our diet was well in excess of her requirements and weight gain could be expected.

2/27/28: Weight $119\frac{1}{2}$ pounds. The diet was again increased and was filled with carbohydrate 175.6, protein 100.4, fat 322, glucose 265.2, fatty acids 335.8, ratio 1.2, calories 3998. This was 122 per cent above her true basal which was 42 per cent above the normal.

3/2/28: Weight 121 pounds. Basal metabolic rate plus 39 per cent.

per cent calories, which would theoretically protect the patient against a weight loss on the assumption that the metabolic rate was plus 50 per cent. Sedatives were administered twice daily, but Lugol's was not given at this time. The basal requirements for a normal patient of the same height, weight, age, and sex were 1267 calories. The diet order as filled contained carbohydrate 90.8, protein 54.8, fat 174.7, glucose 139.8, fatty acids 182.3, ratio 1.3, calories 2154.7 (basal plus 70 per cent).

1/27/28: Admitted; weight $109\frac{3}{4}$; diet instituted and insulin administration begun.

1/28/28: Weight $109\frac{1}{2}$.

1/30/28: Weight $109\frac{1}{4}$.

1/31/28: Weight 107. Basal metabolic rate estimation by oxygen consumption +108 per cent.

2/1/28: Weight $106\frac{1}{2}$.

2/2/28: Weight 106.

The patient desugarized within the twenty-four hours in the hospital. Progressive weight loss continued so that it was quite obvious at the end of six days that the metabolic rate was in excess of 50 per cent even though it might not have been as high as 108 per cent as determined by oxygen consumption.

Period II. Weight Gain under Increased Food and Use of Lugol's Solution.—2/2/28: Weight 106. The indication now was to raise the diet as rapidly as possible without upsetting the patient's tolerance. Diet order, as filled, contained carbohydrate 102.8, protein 72, fat 245.2, glucose 169, fatty acids 252.7, ratio 1.5, calories 2896 or basal plus 129 per cent.

2/4/28: Since the urine remained sugar free, the carbohydrate was increased to 126.8, making a glucose value of 192.3, ratio 1.26, and calories of 2911.

2/6/28: Weight $113\frac{1}{2}$ pounds.

2/10/28: Basal metabolic rate estimation plus 78. This rate appeared to be a more nearly correct one at this time than the 108 per cent, and this was borne out by the feeding experience. With the increased diet the patient was allowed out of bed (ambulatory activity). If her true metabolic rate was plus 78 or 178 per cent of the normal, then she would require

Her condition was good until a week prior to entrance. At this time she caught a cold and on the third day developed a chill. There was increasing cardiac distress for two more days, followed by vomiting and Kussmaul breathing. She was sufficiently recovered from the acidosis on December 3rd to allow us to seriously consider the diagnosis of exophthalmic goiter which had been hovering over her for eleven months. At this time her weight was 105 pounds, whereas her weight on October 14 had been 111 pounds. The loss of 6 pounds in a patient who had been through a diabetic coma could not be considered significant.

The physical examination after recovery from the acidosis revealed a patient who had evidently lost considerable weight. Her eyes were not prominent, the thyroid was easily palpable but not strikingly enlarged. The heart had a forcible beat at the apex. There was a surgical scar in the right upper quadrant. The findings otherwise were not significant.

Clinical Course of Case in Hospital. Period I. Recovery from Coma and Establishment of Diabetic Control.—November 25, 1930: Patient in coma, management instituted. Sodium iodide intravenously and Lugol's per rectum.

November 29, 1930: Diet instituted. Carbohydrate 114.7, protein 59.3, fat 150, glucose 164, fatty acids 161, ratio 0.98, calories basal plus 55 per cent (2046). Fasting blood sugar 235; CO_2 65. Total daily insulin dosages 95 units. Lugol's gtt. xv, t. i. d. continued.

December 2nd: Weight 105 pounds. Basal metabolic rate plus 86.

December 3rd: Lugol's discontinued so that the effect of feeding might be tested.

December 10th: Last day of this period.

Period II. Loss of Weight on Basal plus 30 per cent Calories, Despite the Persistence of Iodide Effect for at Least Seven Days (December 11 to December 19). Activity: Bed Patient with Bathroom Privileges.—December 11th: Weight 105.5 pounds. It is now seven days since the Lugol's was discontinued and its effect would be expected to persist for an-

3/5/28: Weight 125 pounds. Thyroidectomy with relief of thyroid symptoms and improvement of diabetes.

Case II.—Hyperthyroidism Obscured by Diabetes and Diabetic Coma.—This patient, a white female, aged thirty-six, entered the Research and Educational Hospital, November 25, 1930, with a diabetic acidosis. Her past medical history included the usual diseases of childhood, recurring attacks of tonsillitis, and one attack of rheumatic fever. She had several operations on an ankle, which was fractured at five years of age. Her gallbladder was removed three years ago. She had four children, one of whom died during delivery. Her history otherwise was not significant until the onset of her present complaint.

January, 1929, she developed pneumonia from which she did not recover completely. In the spring of 1930 she was admitted to a neighboring hospital with a diagnosis of diabetes and goiter. Here, her goiter was treated with medicine and her diabetes with insulin and diet. Operation was not suggested.

On discharge to the out-patient department, at which time she weighed approximately 130 to 135 pounds, her diet contained 3300 calories. During the summer months, she felt good despite her continued loss of weight. She regularly broke her diet because of "hunger." She stated that the urine did not remain sugar-free.

On October 6 she was admitted to the surgical ward of the Research Hospital with a diagnosis of exophthalmic goiter and diabetes. On physical examination the diagnosis of exophthalmic goiter was not evident. The pulse range during her twelve days' stay fluctuated between 72 and 90, and her basal metabolic rate showed a plus 29 per cent with a pulse of 72 taken at the time of the test. The surgeon considered that her problem was largely a diabetic one, and transferred her to the medical department. To this she demurred, and she was discharged from the hospital. She reentered the medical ward on November 25 with the following story:

calories true basal plus 50 per cent (normal basal plus 110 per cent) 2997.

January 31st: Weight 104. Basal metabolic rate plus 13 per cent.

February 9th: Weight 112 pounds. Thyroidectomy.

The behavior of the patient following the thyroidectomy has abundantly justified the diagnosis of hyperthyroidism.

Comments on this Case.—This patient was observed for eight to nine months in a neighboring hospital and dispensary where numerous metabolic rates were run, without a diagnosis of hyperthyroidism. She was admitted to the surgical floor of this hospital in October, 1930, and remained there twelve days. She was discharged as a diabetic without hyperthyroidism. She was seen on the medical floor by the surgical consultant after the above study was made on January 30, 1931. He still was not convinced that the patient had hyperthyroidism. The presence of the diabetes which is such a common cause of weight loss, and the absence of striking physical signs of hyperthyroidism were the factors which obscured the diagnosis in this case.

Case III.—Hyperthyroidism Obscured by a Suggestive Parkinsonian Syndrome, and a Severe Pain in the Right Arm, Indicative of Brachial Plexus Neuritis.

The patient, a man sixty years of age, entered the hospital on November 25, 1931. His history was not significant until five months ago. At this time he began to be nervous and irritable. He has gradually developed dyspnea on exertion and has become increasingly conscious of his heart. This manifested itself at one time as palpitation, at another as rapid heart action, and at another as pounding.

His appetite had been poor lately and on several occasions he was nauseated following his meals. There was one vomiting spell. When questioned about his weight, he thought that he had lost some weight, but this had not impressed itself upon him. He was quite sure, however, that he was much weaker than usual. He was accustomed to handling storage batteries,

other seven to ten days. Diet: carbohydrate 115 Gm., protein 59, fat 113, glucose 160.7, fatty acids 129.3, ratio 0.8, calories basal plus 30 per cent (1717) calories. Fasting blood sugar 136; CO_2 51; insulin for day 40 units.

December 15th: Weight 105 pounds. Basal metabolic rate plus 65.

December 19th: Weight 106 pounds. Basal metabolic rate plus 43.

December 22nd: Weight 104 pounds. The influence Lugol's had has probably disappeared by this time.

December 29th: Weight 101 pounds. Basal metabolic rate plus 52.

December 30th: Weight 100 pounds. Close of this period.

Period III. Stationary Weight on True Basal plus 30 per cent. Bed Patient with Bathroom Privileges.—December 31: Weight 100 pounds. It was assumed that her true rate at this time was approximately plus 40 per cent or 140 per cent of the normal. A diet 30 per cent above this would be $140 \times 30 = 182$ per cent or basal plus 82 per cent. Diet: carbohydrate 125, protein 70, fat 190, glucose 184.6, fatty acids 203.2, ratio 1.1, calories 2490. Insulin for day 30 units.

January 5, 1931: Weight 101.

January 10, 1931: Weight $101\frac{1}{2}$. Basal metabolic rate plus 30 per cent.

January 15, 1931: Weight $101\frac{3}{4}$.

Period IV. Gain in Weight Begins on True Basal plus 30 per cent (basal plus 82 per cent) after Addition of Lugol's and Continued on True Basal plus 50 per cent (basal plus 110 per cent).—January 15, 1931: Weight $101\frac{3}{4}$. Diet same as Period III. Lugol's gtt. x, t. i. d. Insulin for the day 16 units.

January 19th: Weight $101\frac{1}{2}$.

January 23rd: Weight 101. Basal metabolic rate plus 35 per cent.

January 26th: Weight 102.

January 28th: Weight 103. Diet: carbohydrate 145, protein 80, fat 233, glucose 214.7, fatty acids 246.5, ratio 1.15,

11/27/31. Weight $159\frac{1}{4}$ pounds. Diet basal plus 30 per cent. Calories 2178. Basal metabolic rate estimation, -10 per cent.

11/28/31: Transient attack of auricular fibrillation.

11/30/31: Weight $158\frac{1}{2}$. Basal metabolic rate plus 4 per cent.

12/7/31: Weight 156.

Period II. Weight Loss Stopped on Basal plus 75 per cent Calories. 12/8/31: Diet basal plus 75 per cent, 2946 calories.

12/11/31: Weight 158.

12/13/31: Weight 159. Patient discharged from hospital with the provisional diagnosis of toxic adenoma. The conclusion was based on the loss in weight of a bed patient on basal plus 30 per cent calories. It was assumed that the observed metabolic rates of -10 per cent and +4 per cent were incorrect. The administration of Lugol's solution was begun, the diet increased to basal plus 150 per cent, and the activity changed from bed rest to ambulatory in anticipation of a thyroidectomy.

12/28/31: Reentered hospital.

12/30/31: Weight 164 pounds. Basal metabolic rate +20 per cent. A transitory attack of fibrillation occurred in the afternoon.

1/2/32: Thyroidectomy. A large nodular goiter with a substernal right lobe was removed. This was the evident cause of the pain. Within twenty-four hours the pain in the arm, which previously required opiates, disappeared. Convalescence was slow but complete with relief of all complaints.

Comment.—This patient was suspected of having a Parkinson's syndrome because of the right hand tremor and appearance of his face. These patients frequently lose weight. Because of the intractable pain a brachial plexus neuritis was considered. A pain of this severity could interfere with the patient's appetite, cause a loss in weight, and produce a state of nervousness and general ill health. To these difficulties were added the laboratory findings of -10 per cent and +4 per cent for metabolic rates. However, the feeding results showed

moving them from place to place, and of late he was unable to continue this work.

Within the last three months pain in the right shoulder and forearm had appeared and become so severe that he was sleeping poorly. One of his relatives noticed the marked changes in his appearance and brought him to the hospital for diagnosis and treatment.

On physical examination he had a questionable masked face. His right hand showed a moderate fine tremor at rest. The hands were warm and moist. The pain in the right arm was aggravated on elevation and backward rotation of the arm. The forearm and hand showed some swelling. The right axillary region was tender to palpation, but no glands nor masses were noted. The hands showed a relative coarse tremor on extension, and muscle weakness was definite as shown by his inability to hold the leg extended without support for over forty seconds. The eyes showed no exophthalmos or lagophthalmus. The thyroid gland was somewhat enlarged. The chest on physical and x-ray examination showed a normal-sized heart with prominence of the aortic arch, an accentuation of the first sound at the apex, cardiac rate of 88, and lung markings within normal limits. The blood pressure was 140 systolic, 96 diastolic. The deep reflexes were normal. The abdominals were not elicited, the cremasterics were sluggish. No pathologic reflexes were noted.

The urine examinations were all negative. The blood Wassermann was negative. Blood counts were normal. Plates of the right shoulder and cervical spine showed no bony pathology in the right shoulder. The seventh cervical transverse processes were somewhat longer than normal. The intern, after taking the patient's history and examining him, made a tentative diagnosis of "effort syndrome."

The Clinical Course of the Case.—The studies of the case included the use of diagnostic quantitative diets as previously outlined.

Period I. Loss of Weight on Basal plus 30 per cent. Activity: Absolute Bed Rest.—11/25/31: Admitted.

Case V.—A Case of Essential Hypertension Simulating Hyperthyroidism.—This patient was referred for an opinion on the existence of an hyperthyroidism.

The patient, a white female, age thirty-five, developed headaches and a systolic blood pressure of 220 mm. while pregnant in 1929. Her pulse was rapid (100 to 120) and her urine was negative. Metabolic rates of +25 per cent and +18 per cent were obtained. The blood pressure did not respond to restrictions in diet, but fell promptly after Lugol's solution was administered. Following delivery a metabolic rate of +40 per cent was observed.

On examination (some four months after delivery) the weight was found to be approximately the same as before the pregnancy. The clinical picture resembled that of essential hypertension rather than that of hyperthyroidism.

She was a housekeeper caring for a six-room apartment, running a light vacuum cleaner, dusting, doing her own marketing, cooking, and dish washing. With this amount of work it seemed that a diet with basal plus 50 per cent calories would not contain too much food. If she had any significant hyperthyroidism and continued to do this amount of work, she must lose weight. The weight was 146½ pounds when the diet was started; two weeks later it was 148½ pounds. This furnished conclusive proof of the absence of hyperthyroidism.

SUMMARY AND CONCLUSIONS

A plan of quantitative feeding of patients is described which differentiates obscure cases of hyperthyroidism from other mimicking clinical conditions. In reality this test is the equivalent of a metabolic rate estimation. If the patient loses weight then he has an increased metabolic rate. If the weight is maintained or increased the rate is not elevated.

In applying such a plan certain precautions must be observed.

1. Other causes for weight loss, glycosuria in diabetes, carcinoma, tuberculosis, low-grade febrile infections, or other wasting diseases must be eliminated.

that these rates were inaccurate, and so the tentative diagnosis of toxic adenoma was considered as the probable diagnosis and was substantiated by operation and the further course of the case.

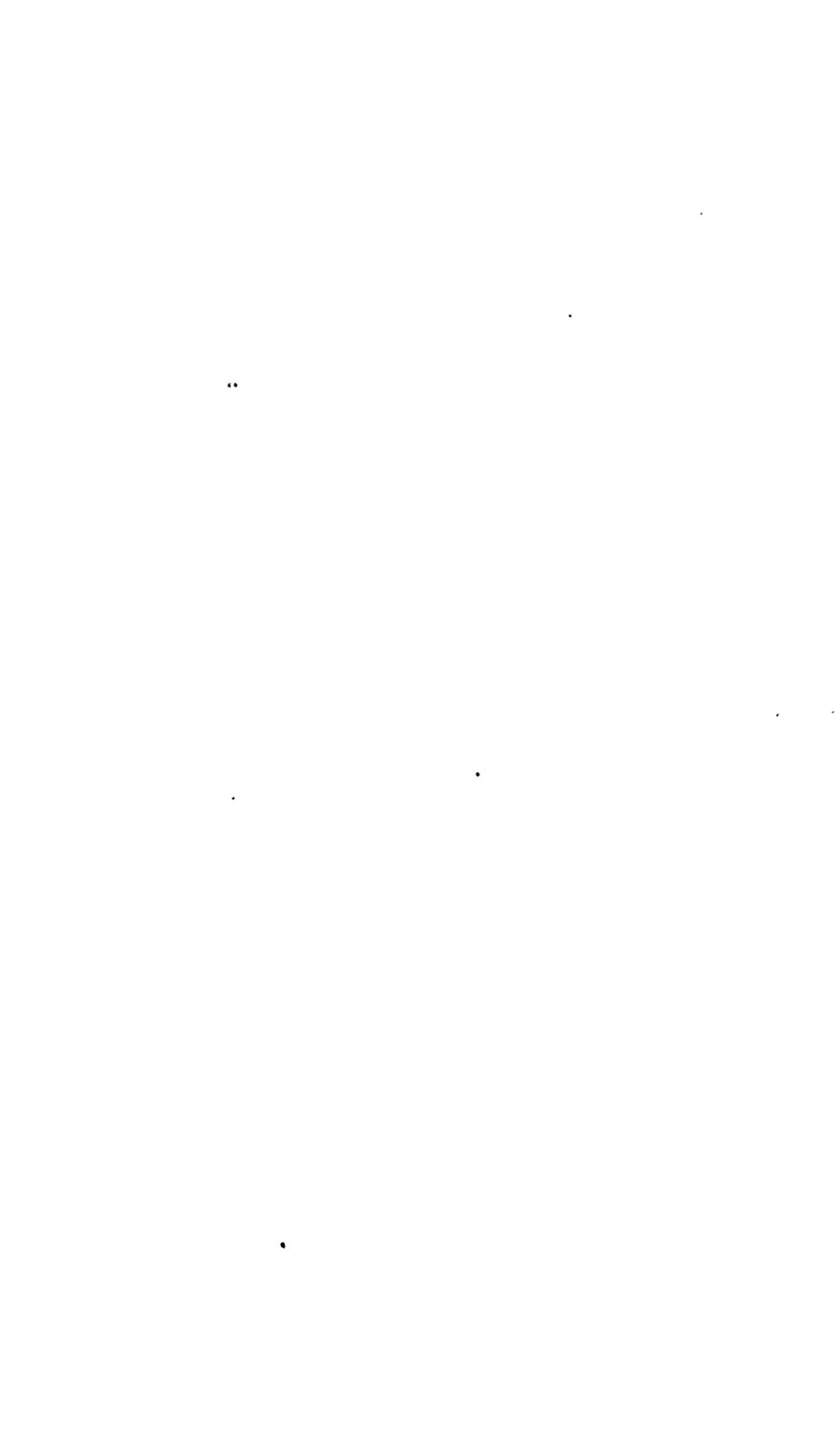
Case IV.—Anxiety Neuroses, Neurocirculatory Asthenia Simulating Hyperthyroidism.—Two cases will be cited as constituting the fourth class of patients concerning whose diagnosis confusion may arise.

(a) A Jewish boy of nineteen years of age entered the hospital with the following complaints: Stomach trouble associated with gas attacks during which the heart beats forcibly and palpitation occurs; loss of 20 pounds in weight, rapid pulse, swelling of neck with choking spells.

After examination a probable diagnosis of "anxiety neurosis and neurocirculatory asthenia" was made.

Metabolic rates on three occasions showed +17 per cent, +12 per cent, +10 per cent. On a diet containing basal plus 30 per cent calories the patient gained 3 pounds in ten days. Hyperthyroidism was considered as excluded. In five to six months he became mentally adjusted and his recovery was complete with a gain of 30 pounds.

(b) A young woman was healthy until marriage five years ago. Since then, financial reverses, a stepmother, and a mother-in-law have proved too much for her. She has found it necessary to spend most of the day in bed to avoid cardiac unrest, choking spells, and prevent weight loss. Her pulse ranges between 96 and 120. Muscular strength is poor. The picture of the hyperthyroidism seemed so definite to the neurological consultant that he was unwilling to discuss her mental problems until a diagnosis of exophthalmic goiter was conclusively eliminated. The metabolic rates +20 per cent, +15 per cent, and +12 per cent, were not entirely conclusive. The feeding test on basal plus 30 per cent showed a gain in weight. She was returned to the neurological consultant, who now has defined her problem although he has not been able to accomplish an adjustment.



CLINIC OF DR. SIDNEY A. PORTIS

COOK COUNTY HOSPITAL

MEDICAL ASPECTS OF THE PREOPERATIVE AND POST-OPERATIVE MANAGEMENT OF GALLBLADDER DISEASE¹

Most internists and especially gastro-enterologists are coming more and more to believe that the surgical aspect of gallbladder disease is playing a more predominant rôle. However, before submitting any given patient to a surgical procedure one must always take into consideration the question of mortality associated with surgical intervention. In the hands of good surgeons certainly no one could ask for improvement in surgical technic, therefore, if the mortality rate is to be lowered in operative interference for gallbladder disease, the management pre- and postoperatively must necessarily play a dominant rôle.

I have been interested for the last five years in developing a medical management that would safeguard these patients who have been advised to have surgery. I am happy to report to you this morning that in this period, in cases other than carcinoma of the gallbladder where operative interference has been deemed advisable, in private practice I have had no deaths. It may be, however, that many of these patients were submitted earlier to operation than the average case of cholecystitis and this is true in a great many cases. I firmly believe that the routine management instituted in these cases is a decided comfort to the surgeon in knowing that these patients are good surgical risks, and those that are not, are amply provided with protective measures to prevent the possible complications that may arise with this type of surgery.

Unless there is an urgent need for operative interference, all patients with cholecystitis are hospitalized three to four

¹ Clinic given to the students of Loyola University Medical School.

days before operation. On entrance they have the usual laboratory work including a complete blood count with differential, a Wassermann and a Kahn test, bleeding and coagulation time, blood chemistry, including nonprotein nitrogen and sugar, icterus index and van den Bergh test. They are also typed for possible blood transfusion with suitable donors at hand at a moment's notice. The urinary picture is watched daily, and an electrocardiogram is made where indicated.

Fortified by this laboratory background the patients are then put on a special preoperative diet which consists of the following:

- Breakfast:* Melba toast with jelly, no butter.
Fresh or stewed fruit.
Cooked cereal with skimmed milk.
One egg.
Tea, chocolate, or cocoa.
- 10 A. M.:* Strained orange juice plus glucose; or malted milk made with skimmed milk, plus glucose or lactose.
- Dinner:* Large serving potatoes, or steamed rice, or noodles.
Two servings of vegetable.
Salad with lemon, no dressing.
Fresh or stewed fruit or simple cereal, pudding or custard.
Melba toast with jelly, no butter.
Tea with sugar, if desired.
- 3 P. M.:* Strained tomato juice or eggnog made with skimmed milk, plus glucose or lactose.
- Supper:* Baked potato or cereal with skimmed milk.
Two servings of vegetables.
Salad with lemon, no dressing.
Stewed or fresh fruit.
Melba toast with jelly, no butter.
Tea with sugar, if desired.
- 8 P. M.:* Skimmed milk and crackers.

If these patients have findings of blood chemistry within range of normal, if their icterus index is below 15, if they show no evidence of bile in the urine and there are no cardiorenal complications, they are then submitted to surgery.

After surgical interference the following routine is used:

Immediately on return to their room they are given for the first six hours inhalations of carbon dioxide for one half to one minute every half hour. For the next six hours they are given similar inhalations every hour, and for the next twelve hours every two hours. The carbon dioxide inhalations may be kept up for the next twenty-four hours if necessary. On their return they are given 1000 cc. of normal saline with 2.5 per cent glucose subcutaneously. If there is no cardiac complication another 500 or 1000 cc. is repeated within a few hours, so that the total amount of fluid intake in the patient in the twenty-four hour period from the standpoint of subcutaneous fluids is approximately 3000 cc. However, in patients with myocardial involvement or patients with evident, definite hypertension the first subcutaneous injection may only be 750 cc. That may not be repeated again for four to six hours. We do not feel that it is justifiable to burden the myocardium with too much fluid at one time because many of these patients may show evidence of a break in compensation, which even though it is mild may lead to passive hyperemia of the lungs which, as you know, is a fertile field for the development of postoperative pneumonia. In some of these patients one may have to resort to proctoclysis by the Murphy drip method in order that an ample amount of fluid may be given to any one individual.

Following the first twenty-four hour period and providing there has been no nausea or vomiting, the patients then may be fed by mouth in the following routine manner:

First day: Tea with sugar.

Second day: Add orange juice.

Third day: Add oatmeal or farina gruels, melba toast with jelly.

Fourth day: Add strained stewed fruits and mashed potato.

Fifth day: Add soft-boiled eggs and milk.

Sixth day: Preoperative diet.

This routine is varied to suit the particular needs of the patient.

During the first four or five days postoperatively daily icterus indices are made to give us some indication of liver func-

tion. In my experience the bilirubin content of the blood stream has been our most important single factor in estimating liver function.

At the end of approximately six days the patients are allowed to sit up in bed and on the seventh day, providing there is no contraindication, they may sit out of bed ad lib. On the ninth day they may try to take a few steps and at the end of the twelfth day in the average case the patient is ready to leave the hospital. However, this is also varied, suiting the needs of the clinical picture of the patient for no rule of thumb can be laid down for handling any particular case. But in the main these general procedures seem to satisfy the needs of the uncomplicated cholecystectomized patient.

These patients are then allowed to leave the hospital on a diet which is similar to their preoperative management and then they are told that for the matter of a month or two they must be on a relatively low fat diet, with some medical management until the pathologic processes associated with their cholecystitic disease has readjusted itself to its near normal. Then they may gradually assume a more regular diet, being careful for some time to keep away from fatty, greasy and fried foods.

The care of the bowel in these patients during their pre- and postoperative management is exceedingly important. I rarely ever resort to any enemata other than simple tap water or oil retention enema. Simple mineral oil by mouth may be given to these patients. I do not feel that drastic catharsis either from above or below is indicated in these patients, because it leaves the bowel in a more irritable state.

Their urinary output is carefully observed and the leukocyte count is made frequently. Their degree of anemia is carefully observed so that no untoward manifestations may develop.

With these measures in mind, I would like to report to you the pre- and postoperative management of three typical cases which demanded surgical intervention, so that you may note how the routine may have been modified in these individual cases.

Case I.—The first case, a somewhat complicated one, is that of a physician, Dr. M., who entered the hospital with the following history.

He was perfectly well until three weeks before admission when he developed pain in the right upper quadrant. The character of the pain was colicky and lasted for varying periods. He never noted any associated jaundice. However, on more careful interrogation he stated that he had been troubled with some belching and flatulence and a feeling of fulness after meals for the last several years. During the last three weeks previous to entrance he had been undergoing examinations for the source of his abdominal discomfort and it was found that he had a nonfilling of the gallbladder, not only by the oral method of cholecystography but subsequently checked by the intravenous procedure. Following the intravenous procedure and apparently thirty-six hours after the completion of the tests he began to have acute upper abdominal pain. It was so severe that he was writhing and tossing about as though he were in extreme agony. This physician had been a former athlete and football player and that made the pain much more real. He was told earlier in the evening to try and see if atropine would not relieve his pain. Four hours after the onset of the acute disturbance he was admitted to the hospital with the above clinical picture and seemed to be very uncomfortable.

His temperature registered 97.6° F., with pulse of 62 and respirations of 20. Physical examination at that time revealed that the right upper abdominal quadrant was exceedingly rigid and the patient seemed to be extremely restless. Atropine hypodermically had no effect on the pain. The leukocyte count was 14,500, of which 84 per cent were polymorphonuclears and 16 per cent lymphocytes. The urine at that time showed no bile and was otherwise negative.

Because of the excruciating pain that this patient presented, operative interference was deemed advisable six hours after the onset of the attack. At operation the following pathology was found: The gallbladder was found high up in the abdomen

underneath the costal arch, greatly distended, dense and green to black in color. There was a serosanguinous exudate in the peritoneal cavity. Cholecystectomy was deemed advisable and the following is the pathologic report:

Acute suppurative cholecystitis superimposed on a chronic cholecystitis; cholelithiasis. The gallbladder measured $7 \times 3.5 \times 3.5$ cm. The wall was thickened, grossly granular and discolored green; in the fundus, yellow papillary projections of mucosa, 5 mm. in diameter, noted. There were no stones or ulcerations. Microscopical examination revealed that the wall of the gallbladder was thickened by edema, with a few indurations, with many neutrophils, eosinophils, periblasts, and histiocytes, and with diffuse increase in connective tissue in the mucosa and muscularis. The mucosa for the most part was injected but there were a few focal erosions. The muscularis in a few portions showed necrotic changes. In one area the mucosa formed papillary projections with large vesicular cells, with firm cytoplasm in the subepithelial layer. In a few areas the muscle fibers showed necrotic changes.

This serosanguinous exudate is significant of an early gangrene of the gallbladder and for that reason the postoperative management of this case was fraught with danger.

Immediately following operation the patient was returned to his room in the surgical environment as discussed above and was given in addition to the usual amount of glucose and normal saline subcutaneously, 25 Gm. or 50 cc. of a 50 per cent glucose solution intravenously, with 5 units of insulin at the same time. This glucose intravenously, was repeated the next day and again on the third day, in spite of the fact that the patient was able to take nourishment by mouth.

For two or three days the patient's clinical course was apparently uneventful. However, three days following operation his icterus index which remained within 10, 12 or 15 very rapidly rose to 33, with evidence of a bile-stained conjunctiva and urine. He was not nauseated however, and it was thought wise at this time to give him some more intravenous glucose and watch the further course. His icterus index the next day

was 25, and the following day was 12, and one week after surgical intervention it was 9.

This patient made an uneventful recovery and is perfectly well and happy today.

In this particular case our only concern was adequate protection for the liver. There is no question in my mind that even though the patient developed bilirubinemia with adequate postoperative management the changes would probably have been more marked had we not increased the carbohydrate reserve of the liver. This liver damage following surgical interference is one of the most important complications that may present itself. I know of no better way of protecting the liver against these very devastating changes than the adequate use of glucose. It seems in these particular patients the glucose given subcutaneously or intravenously has a much better chance of protecting the liver than carbohydrate given by mouth. If we are to prevent the development of acute hepatic insufficiency, which when it does develop, is practically always 100 per cent fatal, we must bear in mind that the liver and its glycogenic function play a very predominant rôle. The protection of the glycogenic reserve seems to go hand in hand with the protection of the other very important functions of the liver. A great many of the postoperative deaths associated with surgical interference in bile tract disease may be accounted for, when they develop four or five days postoperative, on the basis of overwhelming liver damage. It is also well to bear in mind that unless we are dealing with a case of obstructive jaundice that operative interference in the presence of bilirubinemia may not be a wise procedure. If there is an associated bilirubinemia in these cases and there is no immediate need for surgical interference, these patients should be at quiet and rest, with high carbohydrate, low fat intake. I have found it particularly advisable in this group of cases to give them small doses of potassium iodide, 5 to 10 grains three times a day, in addition to their other medical management for the icterus. It seems that potassium iodide breaks down the changes in the liver cells which are a barrier to the normal mechanism of the se-

cretion of bilirubin into the biliary ducts. Particularly is this true in those cases of hepatitis associated with cholecystic disease. Occasionally, I have used simple cholagogues, as effervescent sodium phosphate or magnesium citrate in the morning. I do not feel that such drastic purgatives as magnesium sulphate or similar therapeutic procedures are distinctly advantageous to this type of patient. There are innumerable other cholagogues that have been advocated. Some of them are effective in some cases, while in others they are hopelessly felt wanting. It seems to me that the simpler the measures used the more rational will be your evaluation of the complications that might present themselves.

Case II.—The second patient I would like to present to you has been under my observation for some time. She is a known cardiorenal, aged fifty-eight years. The cardiac symptoms have entirely predominated. The gastro-intestinal manifestations have been exceedingly mild and for the most part have never made themselves very evident until one day she developed an acute right upper quadrant pain which brought in a differential diagnosis of acute distention of the liver incident to a passive congestion of the heart, coronary occlusion, and an acute gallbladder. There was not sufficient evidence to make the first two diagnoses, and with the temperature, leukocytosis and other findings it seemed that a diagnosis of suppurative cholecystitis was justifiable.

I need not take up your time with a detailed history of the clinical story. The patient had been suffering for three or four days previous to my seeing her and had been taken care of by her family doctor. When she entered the hospital she had an icterus index of 15. She had a leukocyte count of 20,400, with 86 per cent polymorphonuclears, 9 per cent lymphocytes, 5 per cent monocytes, red blood count 4,620,000 and hemoglobin 80 per cent (Sahli). The leukocyte count averaged between 20,000 and 21,000 for the first twenty-four hours, and the next day it went down to 18,500. Her temperature was 101.4° rectal, pulse 112, respirations 24. The urine showed some albumin,

was 25, and the following day was 12, and one week after surgical intervention it was 9.

This patient made an uneventful recovery and is perfectly well and happy today.

In this particular case our only concern was adequate protection for the liver. There is no question in my mind that even though the patient developed bilirubinemia with adequate postoperative management the changes would probably have been more marked had we not increased the carbohydrate reserve of the liver. This liver damage following surgical interference is one of the most important complications that may present itself. I know of no better way of protecting the liver against these very devastating changes than the adequate use of glucose. It seems in these particular patients the glucose given subcutaneously or intravenously has a much better chance of protecting the liver than carbohydrate given by mouth. If we are to prevent the development of acute hepatic insufficiency, which when it does develop, is practically always 100 per cent fatal, we must bear in mind that the liver and its glycogenic function play a very predominant rôle. The protection of the glycogenic reserve seems to go hand in hand with the protection of the other very important functions of the liver. A great many of the postoperative deaths associated with surgical interference in bile tract disease may be accounted for, when they develop four or five days postoperative, on the basis of overwhelming liver damage. It is also well to bear in mind that unless we are dealing with a case of obstructive jaundice that operative interference in the presence of bilirubinemia may not be a wise procedure. If there is an associated bilirubinemia in these cases and there is no immediate need for surgical interference, these patients should be at quiet and rest, with high carbohydrate, low fat intake. I have found it particularly advisable in this group of cases to give them small doses of potassium iodide, 5 to 10 grains three times a day, in addition to their other medical management for the icterus. It seems that potassium iodide breaks down the changes in the liver cells which are a barrier to the normal mechanism of the se-

tive course her pulse was between 70 and 90. The digitalis was kept up postoperatively and the same measures as instituted in the previous case were employed in this patient.

The pathology at operation showed a very definitely involved gallbladder. The pathologic diagnosis was: Microscopical: acute suppurative and chronic cholecystitis with much granulation tissue and cholesterosis, the presence of a foreign body reaction with many giant cells. There were also numerous calculi found in the gallbladder.

I am presenting this particular patient to you because it brings up some very important medical considerations which must be very carefully analyzed before submitting this patient to operation. It is interesting to note that the bilirubinemia subsided, so there was evidence that the liver changes were not predominant and that the process had become well walled off in the gallbladder. Secondly, this patient with her high leukocytosis indicative of a suppurative process brought up the question very seriously of whether any immediate surgery should be undertaken or simply conservative measures to allow the process to be quiescent. This was, of course, very materially involved in the question of the cardiac picture. Knowing previously that this patient had been fibrillating and that she had a very definite myocardial disease, it seemed much more justifiable to play a rôle of watchful expectancy in the hope that the myocardium would be markedly improved before we had to submit her to surgery. For this reason the patient was digitalized preoperatively. While there was no outward evidence of a break in compensation and many cardiologists may not think it justifiable to give this particular type of patient digitalis, in my own personal experience it has seemed much better to have the heart muscle fortified with a little digitalis for a period of days preoperatively so that it can withstand the burden of a surgical procedure. This is well justified when one considers the result obtained in this patient who was such a poor surgical risk with a badly damaged myocardium. The pulse postoperatively for the most part was between 70 and 80 and on one occasion it reached 90. It seems to me that

some acetone but no bile was present and no sugar. The albuminuria was explained on the presence of an occasional red blood cell and some finely granular casts. Her blood pressure was 170 systolic and 80 diastolic. The nonprotein nitrogen was 32 and blood sugar 80.

An electrocardiogram at that time revealed a PR interval of 0.16 second; left axis shift. QRS was slurred in leads II and III. T was diphasic in lead I and inverted in lead III which was compatible with her myocardial disease. On a previous electrocardiogram taken some months before there were similar changes except that at that time there was an interpolated ventricular extrasystole in lead III and several runs of auricular extrasystoles in lead II, and a left ventricular preponderance.

A flat plate of the abdomen at this time revealed that she had multiple gallstones. The right diaphragm was slightly higher than the left. However, there was no evidence of fluid and there was no suggestion of subphrenic abscess.

Her temperature remained elevated for a period of about six days following entrance into the hospital. The leukocyte count gradually came down within a period of six days to 13,650.

On entrance she was immediately put upon a gallbladder régime as there was no emesis. She was given in addition glucose, 25 Gm., with 5 units of insulin intravenously. Also at the same time 1000 cc. of normal saline with 1 ampule, 25 Gm., of glucose, were given. Because of her bilirubinemia and because of the fact that she had a cardiac manifestation and had developed some arrhythmia it was thought wise to put her on small doses of potassium iodide as suggested previously, and in addition tincture of digitalis.

This patient was kept under observation for a period of sixteen days in the hospital before she was subjected to any surgical procedure. During the period from her entrance to operation her blood pressure had varied from 170 to 190 and just previous to operation it dropped down to its original 170. She entered the operating room with a pulse of 108. However, it is interesting to note that throughout the whole postopera-

85 diastolic. She was markedly tender over the region of the gallbladder. The liver was slightly enlarged. There were no noteworthy findings elsewhere in the abdomen.

From a laboratory standpoint, her basal metabolism rate was -8 , blood sugar 97 mg., nonprotein nitrogen 40, and icterus index was 6. An electrocardiogram showed a rate of 70, regular rhythm, and left ventricular preponderance. The urine examination was essentially negative as was the stool, and there was no occult blood. Stomach acidity was 35 free and 55 total on motor meal with no evidence of retention; free acidity of 20 and total acidity of 30 in an Ewald meal. Blood examination showed 85 per cent hemoglobin (Sahli), 4,500,000 red cells, 6200 leukocytes, with 42 per cent small lymphocytes, 48 per cent polymorphonuclears, 2 per cent eosinophils, 2 per cent basophils and 2 per cent transitionals. Wassermann and Kahn tests were negative.

Plates taken of the spine both dorsal and cervical showed evidence of a hypertrophic osteo-arthritis.

A cholecystogram, oral method, showed at the end of twelve hours a faintly outlined and somewhat mottled gallbladder; at sixteen hours, similar findings, and at eighteen hours the persistence of the faintly outlined gallbladder with a slight thickening along the inner aspect of the gallbladder near the neck.

Fluoroscopical observation of the lungs and the rest of the gastro-intestinal tract showed no noteworthy findings except a slight narrowing of the antrum of the stomach. However, radiographic evidence showed no definite lesion here.

In considering this patient's clinical picture, certainly her age and hypertension would mitigate against any question of surgery. However, with the inability of the gallbladder to give us a cholecystogram within the range of normal and in spite of the icterus index of 6, with her profound weakness and loss of weight, it was thought justifiable to put this patient in the hospital at bed rest for a period of a week or more in order that her blood pressure and cardiac picture might improve. She agreed to enter the hospital.

too many of us too often wait for an actual break in compensation before using digitalis as a preoperative procedure. It may be much wiser to have slight digitalization as a working basis and later when more heroic means are necessary, the results are probably much more prompt, and may in many cases save the patient.

The postoperative course was practically uneventful. She probably had as smooth a convalescence as I have seen in any type of gallbladder surgery, when one takes into consideration the multiplicity of factors concerned in handling this patient. This patient has gone on now for a period of nine months with no recurrence of her abdominal symptoms, although the cardiac picture has again played a somewhat prominent rôle, but that has lent itself to ordinary therapeutic measures.

I am particularly happy to present this type of case because it presents a condition with many complications which the average surgeon without adequate medical treatment would be very much concerned over the outcome of any surgical interference.

Case III.—The third patient I would like to present is an unusually interesting case in that this woman, sixty-four years of age, came in complaining of epigastric pain, cramps, constipation and loss of weight. For the past four years she has been suffering with dull epigastric pain occurring one to two hours after meals, not particularly relieved by food. About every four to six weeks she had severe, colicky epigastric pain which radiated to the back and scapular region. There had been no melena, no hematemesis, no jaundice. She has been markedly constipated and has been using oil. She has lost 8 pounds in the last four weeks, which she attributed to the fact that she was afraid to eat. As far as the inventory of systems is concerned, it is practically negative except that she has noticed some weakness.

Physical examination revealed that the second aortic tone was markedly accentuated. There was a systolic murmur at the base of the heart. The blood pressure 190 systolic and

that her pressure came down within range of normal and made her a fairly good surgical risk, and subsequent postoperative course essentially uneventful. There was no evidence of metastases at that time and the likelihood of this patient having a complete recovery from her carcinoma of the gallbladder is not so remote.

This routine which I have outlined to you in these cases has been followed now for four and one half to five years. It is modified with the individual needs of the patient. A certain group of patient, particularly the group of individuals who come in with low blood pressure and hypothyroidism, and subsequent tendency to develop thrombophlebitis, may be given for a short or long period as a preoperative measure small doses of thyroid in order to "whip up" the circulation and prevent the possibility of thrombophlebitis developing.

A word about the use of carbon dioxide. Abdominal operations in and about the diaphragm are very frequently associated with localized atelectasis of the lungs. Hyperventilation with carbon dioxide expands these atelectatic regions and prevents the development of postoperative pneumonia. Since we have been using this routinely in our group of gallbladder cases, we have had no postoperative pneumonia. It may be that we have been particularly fortunate. I do not mean to imply that one can absolutely prevent the development of postoperative pneumonia by this therapeutic procedure. However, it is a justifiable postoperative procedure and when adequately carried out gives more adequate protection against the development of pneumonia.

An important consideration which I would like to have you remember is, that many cases of gallbladder disease should be submitted to surgery earlier and that one should not procrastinate medically when there may be a definitely surgical aspect. You should also remember that the complications of gallbladder disease as far as surgical interference is concerned are not so much primarily associated with errors in surgical technic but the mortality is raised by the complications that set in because the patient has not had adequate pre- and post-

At the hospital her blood chemistry findings were again checked. This time, however, the blood sugar was 84, non-protein nitrogen 29, cholesterol 410, icterus index 13. The van den Bergh, both direct and indirect, showed a delayed reaction.

The clinical picture during the time she was in the hospital on preoperative gallbladder management showed no noteworthy findings. She was then submitted to surgery. Her immediate postoperative course was uneventful. Once during the course of her stay in the hospital and forty-eight hours after operation she showed a slight febrile reaction which was associated with slight urinary infection, which subsided and the patient made an uneventful recovery.

At operation the following pathology was found: The patient had a small, somewhat thickened gallbladder, showed evidence of calculi, but no outward involvement other than that of the wall of the gallbladder. Within the gallbladder after it was opened there was a small nodule in the mucosa near the neck with no gross involvement of the serosa. There were numerous calculi. The pathologic diagnosis in this particular case was adenocarcinoma of the gallbladder and cholelithiasis.

During her stay in the hospital both pre- and postoperatively her blood pressure came down between 150 and 160. She had a more or less uneventful course.

I am presenting this third case because of the fact that here is a patient with a very definite hypertension, with evidence from the cholecystogram of gallbladder disease, and a remote possibility that this patient with her weakness and loss of weight may have an early carcinoma somewhere in the gastrointestinal tract that could not be definitely diagnosed but apparently was not in the stomach or bowel, seemed to justify the question of surgical interference. The findings at operation more than justified any risk that we took in submitting this particular patient to surgery. In this case instead of having the patient rest in bed for three days preoperatively with this hypertensive picture she was put to rest for at least a week. She had adequate opportunity to adjust herself to the diet, so

operative management. Certainly, if we are to advise surgical interference in many more cases of gallbladder disease, earlier or even later, and particularly in patients who are not good surgical risks, then it is justifiable to insist upon adequate medical management in this group of cases. Our surgeons are coming more and more to believe that if they are to lower their mortality which may be associated with operative interference in gall tract disease, the responsibility must necessarily lie with the medical men in giving the patient adequate protection for what might develop following operative interference. This I hope I have done in giving you a résumé of my method of approach in handling these patients.

practitioner entered the sick room, gave the ailing infant scant attention and concentrated entirely on the diaper. Should there be an excess of fat in the stool he diagnosed fat indigestion and ordered skimmed milk. Were lima-bean-like curds in evidence he diagnosed difficulty with the casein and ordered extreme dilutions—a fundamental of the old percentage system of feeding. Should the iodine test show an excess of starch granules he diagnosed starch indigestion and removed that constituent from the diet. Such superficial effort at attempting scientific diagnosis led only to disaster, and infant mortality remained astonishingly high. The offending fat, starch or protein might be removed from the diet, the stools might regain their consistency and even appear normal, but invariably the children died—the death of inanition. The doctor had treated the stool, but starved the baby.

You know the names of Czerny and Finkelstein. Czerny was the first to suggest that certain cases of constipation were due not to definite intestinal disease but rather to a disturbance of general body metabolism. Finkelstein carrying the work much farther entered the unknown realm of diarrheal disease. To make a long story short Finkelstein spent many years of his life elaborating the theory that much of the then prevailing diarrheal disease was due not to infected milk nor to indigestion, but to a metabolic disturbance in the body induced by improper combinations of cow's milk. There was something in cow's milk—he did not know what—which predisposed to this metabolic disturbance. If unchecked this led to a real disturbance of nutrition. The nutritional disturbance after some days or weeks led to intestinal conditions favoring the fermentation of carbohydrate. The acids formed from such fermentation irritated the intestine and produced diarrhea. Let me emphasize that this intestinal reaction was not considered primary indigestion but was secondary to the development of a general disturbance of nutrition. The primary disturbance was the metabolic injury effected by cow's milk. Hence the reason for milk dilution—to lessen the intensity of the hypothetical offending factor. Only after metabolic injury

CLINIC OF DR. JESSE R. GERSTLEY

MICHAEL REESE HOSPITAL AND NORTHWESTERN UNIVERSITY
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INFANT NUTRITION: BACK TO FIRST PRINCIPLES

HERE are three normal infants. One has been fed breast milk, another a mixture of cow's milk, water and lactose, and the third cow's milk, water and a maltose dextrin preparation. Each child has received orange juice and cod liver oil. I dare say that none of you could tell which one is the breast fed. Some time ago I held a clinic on the normal infant.¹ This will not be a repetition.

Today's subject is one which makes me smile at myself. I intend to violate all my own teachings and precedents and discuss a clinical sign which I have always held relatively unimportant, namely the infant's stool.

Notice this stool of the breast fed. It is soft, almost watery, homogeneous, shiny and of yellow color. The odor is slightly acid and not at all unpleasant. The stool of the infant on the lactose mixture closely resembles that of the breast fed except that it contains a few white particles—perhaps casein curd. However in appearance, consistency color and odor it is much like the former. The stool of the infant receiving the dextrin preparation is entirely different. It is formed, drier, of a darker color and has a slightly putrefactive odor.

What is my object in presenting these specimens and what story do they tell?

I hardly know how to begin. Some thirty years ago when it was considered a distinguished accomplishment to keep a baby alive on artificial feeding, all disturbances associated with diarrhea were considered due to gastro-intestinal disease. Stool examination became of the utmost importance. The

becomes an index of what is going on in the intestinal tract, but in relation to the problem of the nutrition of the entire child its importance fades into insignificance. The condition of the baby as a whole is now interpreted not by stool examination but by direct clinical examination in conjunction with the weight curve.

Finkelstein and Meyer devised albumen milk with its high casein, low whey, low lactose and maltose-dextrin addition in order to reduce intestinal fermentation. But Finkelstein emphasized first, foremost and always, that every treatment must be directed with a view to the welfare of the baby as a whole.

Whether the conception of a primary metabolic disturbance is correct or not time will tell, but unquestionably the changed viewpoint as to treatment—the focusing of the physician's eyes away from the diaper and toward the baby—has been the most powerful factor in reducing infant mortality that has developed in the whole history of pediatrics. I believe in years to come, this one contribution alone will be sufficient to bring Finkelstein the everlasting gratitude and appreciation which his country has always denied him.

This same principle I have found useful in the treatment of almost every medical condition. Those of you who have followed my writings know how I have employed it in the treatment of nutritional disturbance, vomiting, pyloric stenosis and eczema.² Those who have attended my clinic have seen me apply it happily to the treatment of hemorrhagic nephritis and practically every ailment that comes to us. Aldrich³ used exactly the same principle in treating chronic nephritis. It is a principle which has revolutionized the whole theory of pediatric treatment. From the original conception, "the baby is more important than the stool," I have enlarged my philosophy to include the treatment of all clinical entities under the old axiom, "The whole is greater than any of its parts."

But now to return to the infant's stool. Some ten years ago I thought it would be a nice idea to prove or disprove the importance of excessive carbohydrate fermentation in the intestine as a cause of diarrhea. It was not my object to go into

resulted did intestinal fermentation develop to an alarming intensity.

The metabolic conception of diarrhea has been accepted by many, rejected by others, but whether accepted or rejected, all schools have acquiesced in the idea that carbohydrate fermentation whether primary from indigestion or secondary to nutritional disturbance leads to diarrhea. The sugar most easily fermenting then became an object of special study. For thirty years practically all pediatricians have accepted the idea that lactose is the most fermentable of sugars and mixtures containing starch or dextrin the least fermentable.

No one specified whether this hypothetical increased fermentation caused simply an increased production of acid, or an acid of greater intensity. However the impression given by the voluminous literature is that the fermentation leads to acids of greater strength. Moro was the only one to suggest other possibilities. To him, neither the quantity nor the degree of acidity was as important as the location. If acid fermentation existed in the duodenum, diarrhea resulted; if lower down in the intestine, it was to be considered normal.

Parenthetically this theory of diarrhea resulting from carbohydrate fermentation tended to do away with the prevailing ideas of fat diarrhea or starch diarrhea. The fat or starch in the stool became of no etiologic significance. They were simply inactive substances swept out by the rapid peristalsis resulting from the acids of carbohydrate fermentation.

A direct development or corollary of Finkelstein's work led to an entire change in the treatment of diarrheal disease. If the diarrhea is only one of many symptoms resulting from a general metabolic derangement then of course the treatment must be directed not at the symptom but at the main cause. In other words the logical deduction is to treat the baby first and the stool second. Of course, even if the diarrhea is due to a nutritional disturbance, the diarrhea itself if sufficiently severe is also a factor in injuring the patient. Hence the diarrhea must be stopped, but stopping the diarrhea is by no means treating the underlying condition. The condition of the stool

erate amounts of lactose added to cow's milk often cause an increased production of acid but this is so neutralized in the intestine that the *degree* of acidity never nearly reaches that of breast fed. Many of the babies on these mixtures had diarrheas with frequent watery stools, but these diarrheas were induced by factors utterly independent of the diet and recovery occurred with no change in feeding. Putting a baby unaccustomed to the procedure on a metabolism bed resulted in frequent watery stools. A coincidental bronchitis produced a violent diarrhea and an increased excretion of acid, but recovery occurred with improvement in the bronchitis and with no change in diet. To my amazement even these diarrheal stools never reached in degree the high acidity of those of the breast fed. The diarrheas gave no indication of increased intensity of fermentation. If there were increased production of acid much of it was neutralized and the *degree* of acidity was certainly reduced by the various factors influencing it during the passage through the intestine.

I became more reckless. If severe intestinal fermentation did not result with milk dilution why not try whole milk? Nothing followed. Why not add lactose to whole cow's milk? Summarizing another two years' work to my astonishment I found that when the amount of lactose had been increased cautiously to 12 per cent, the stools in respect to appearance, consistency, odor and acidity began to resemble those of the breast fed. I puzzled over this for a long while, first refusing to believe it, until it finally occurred to me that cow's milk had 4 per cent protein and 4 per cent lactose. Adding another 12 per cent lactose gives a mixture with 16 per cent. This gives a relation of lactose to protein of 4 to 1 which is close to the relationship existing in human milk. Here was an interesting thought. I do not know whether this explanation is correct but the facts usually are: This combination does not lead to quite the degree of acidity nor are the findings as uniformly constant as in breast feeding but still the stool is the nearest approach to that of the breast fed I have ever seen develop on any type of artificial feeding.

the larger subject of whether there is a primary metabolic injury to the body by cow's milk, but simply to see if there is an increased intestinal fermentation of carbohydrate in cases of infantile diarrhea. This, I thought, would be relatively simple. If carbohydrates and especially lactose ferment into certain acids, it would be a simple matter to offer an infant a mixture of cow's milk with a known amount of carbohydrate, determine the amount of acid in the stool, then give an increased amount of carbohydrate until diarrhea resulted and then redetermine the amount of acid in the stool. If there were an associated increase in the amount of acid excreted following the increased intake of carbohydrate, this phase of infant nutrition could be settled conclusively and finally. The simple study which I thought could be settled within a few months has taken ten years. It is by no means complete, but becomes ever more absorbing and complex.

Let me summarize briefly the work of these years.⁴ Inasmuch as lactose was considered the most fermentable sugar, I naturally selected it as the carbohydrate to be used. Proceeding very cautiously, the first work was done with dilutions of cow's milk. Studies included the different types of acid excreted as well as the weights and hydrogen ion concentration of the stools. My first idea was that in a mixture of cow's milk lactose might ferment into different and more irritating acids than when in breast milk. For the first few years the results were very confusing. It was very difficult to find any relationship whatsoever between the amount of lactose added to cow's milk and the type of acid or amount of acid excreted in the stools. At times mixtures low in lactose led to greater excretion of free and bound acids than those with higher lactose contents. There is no question that in diarrhea the stools of the babies fed cow's milk are often much heavier than on breast feeding. At such times they contain a greater total quantity of acid free and in combination than the breast fed, but the *degree* of acidity as evidenced by the hydrogen ion concentration is never as great as in breast feeding. Gram for gram the stool on cow's milk feeding contains less acid. Mod-

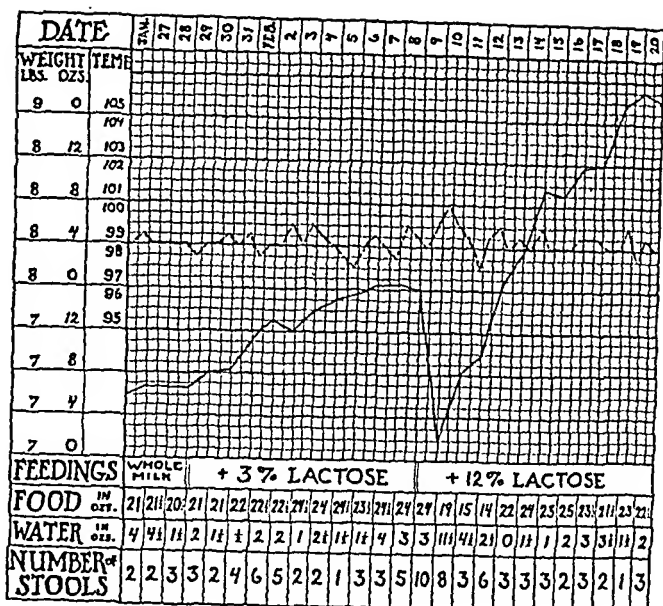


Fig. 275.—This and Fig. 276 show that a diet of whole cow's milk with the addition of 3 per cent. and later 12 per cent lactose continued over a number of weeks led to a severe loss of weight but with no diarrhea. (Jour. Amer. Med. Assoc., Oct., 1930.)

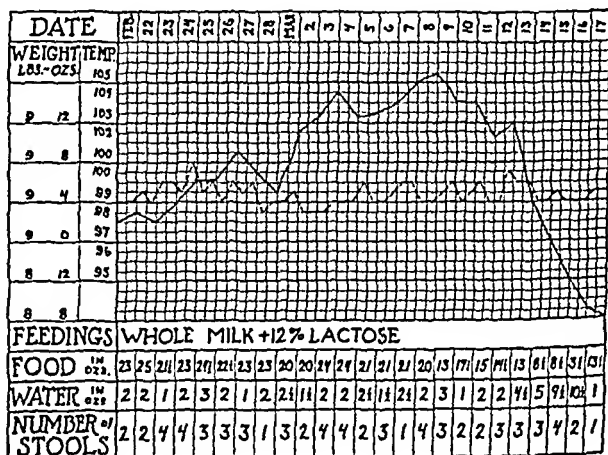


Fig. 276.—This and Fig. 275 show that a diet of whole cow's milk with the addition of 3 per cent and later 12 per cent lactose continued over a number of weeks was followed by a severe loss of weight but with no diarrhea. A disturbance of nutrition following overfeeding. (Jour. Amer. Med. Assoc., Oct., 1930.)

The next step was to determine the reaction of the fecal flora. In another two years we learned that the addition of 12 per cent lactose to whole cow's milk leads to a transformation of the gram negative intestinal flora of cow's milk to the gram positive flora of the breast fed. Again like the chemical findings the bacterial change is not absolutely constant but it is quite definite. For some reason a minimum of two weeks is required for the establishment of both the chemical and bacterial change. Literature has its "Three Weeks" but pediatrics has its "Two."

Now to go back to the clinical picture and to return to the "baby first" idea. Infants receiving such high caloric mixtures, either lactose or maltose-dextrin, gained very rapidly for a time. Had the physician been guided entirely by inspection of the stool, he would have been well satisfied with the baby's welfare. But lo and behold, after some period of rapid growth the infants gradually ceased gaining and soon proved vulnerable to incidental infections to which they reacted in violent manner (Figs. 275, 276, 277). Some sort of nutritional disturbance had been created which led to extreme loss of weight and grave symptoms from slight causes. Here again we had been treating the stool and not the baby. In olden days the doctor treated the stool by starving the baby; the stool improved but the baby died of inanition. Now we were creating a diet which led to an apparently perfect stool but a diet which injured the baby by overfeeding.

It became apparent that these mixtures must be diluted and it is interesting to note that in our dilutions we arrive at mixtures which most pediatricians by practical experience have found most efficacious. However, these dilutions by no means lead to the same stool chemistry and bacteriology as does the whole milk mixture. There is some other factor involved—a study which I am conducting at present.

One day my technician in consternation reported that the chemical findings had changed mysteriously but very definitely. A careful investigation revealed no slips in technic but did disclose that a new dietitian had inadvertently substituted a dex-

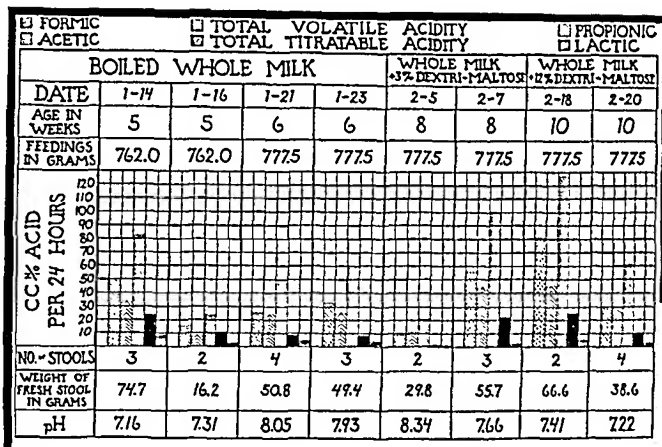


Fig. 278.—The influence of the addition of 3 and of 12 per cent of the maltose-dextrin preparation to whole boiled cow's milk, on the quantity of feces, the frequency of defecation, the excretion of total volatile acids and their salts, on total titratable, lactic acids and lactates, and on the hydrogen ion concentration, in a normal infant. (Jour. Amer. Med. Assoc., Oct., 1930.)

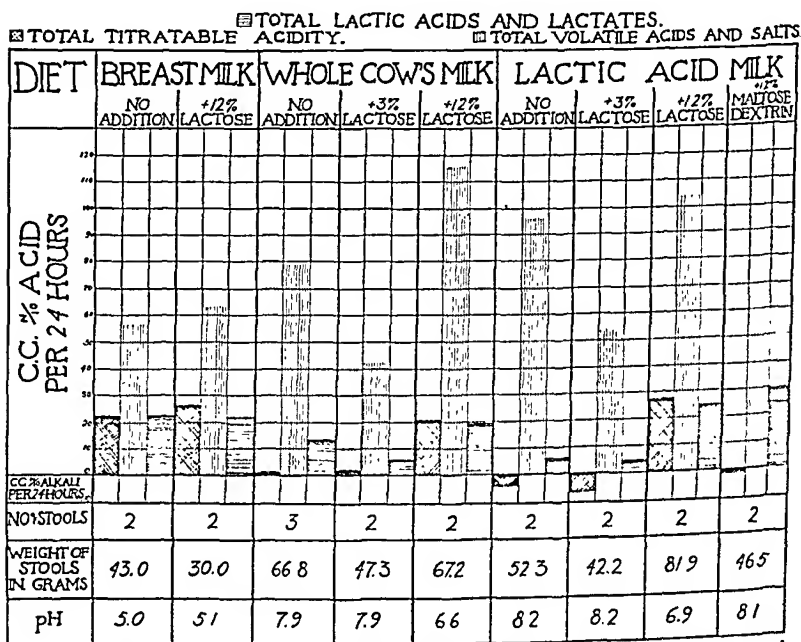


Fig. 279.—The average of all the determinations of total titratable, total free and bound volatile and total free and bound lactic acids and hydrogen ion concentration on the twenty-four hour stool specimens. (Amer. Jour. Dis. Child., March, 1933.)

trin mixture for lactose. Further studies confirmed this original observation (Fig. 278). Chemical and bacterial observations showed very clearly that babies fed cow's milk with maltose dextrin addition have stools which are much less acid than those of the breast fed and a flora which is entirely like that on feedings of simple undiluted cow's milk.

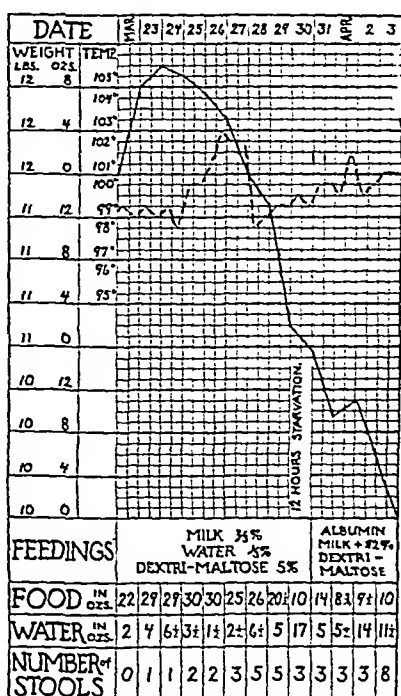


Fig. 277.—Alimentary intoxication induced by a very mild otitis media in an infant who had been on whole boiled cow's milk with 12 per cent of the maltose-dextrin preparation over a period of weeks. Diarrhea occurred only as a terminal complication. (Jour. Amer. Med. Assoc., Oct., 1930.)

We next studied the effects of adding lactic acid to cow's milk (Fig. 279) and found that the addition of lactic acid had no effect whatsoever upon the chemical or bacterial findings. In the determinations made, lactic acid milk gives a stool identical to that of whole cow's milk. Adding 12 per cent of maltose dextrin causes no change. Adding 12 per cent lactose

former, apparently closely correlated to the size of the stool, may result from increased acid formation. But as this acid is mostly bound or neutralized during its journey through the intestine the actual *degree* of acidity of the stool is low and the acidity itself cannot be a factor causing the diarrhea. Perhaps normally this same amount of acid is formed but is absorbed, while in the diarrhea it is swept out. Again maybe Moro was right and the location of the acid in the intestine is the important factor. At times it has seemed to me as if the body were adjusting its water balance and by discharging fluid from the tissues into the intestine was simply washing out the contents—the stools being an index of the conditions then existing in the intestinal tract. At any rate the idea of the danger of excessive acidity in these cases must be given up. All I can say at present is that if lactose is increased to a certain proportion, the stools begin to resemble those of the breast fed.

In this respect it is interesting to note that in our fear of carbohydrate fermentation we have resorted to feedings which tend to constipate. We have completely overlooked the experimental control given us by nature—the normal breast-fed infant. We have completely overlooked fundamental basic observations as to the nature of the stool of the breast fed. In our anxiety to avoid diarrhea from fear of hypothetical excessive intestinal fermentation we have resorted to artificial feedings which give distinctly abnormal intestinal reactions and on the other hand when we give artificial feedings which lead to soft or even loose stools much like those of the breast fed we have become unduly alarmed and feared we were injuring the patient. As I look back over these past years I realize the tremendous rôle played by the carbohydrate fermentation theory in influencing the campaigns to reduce infant mortality. It is laughable to see the horror upon the faces of the interns and nurses when an artificially-fed baby has a stool which resembles that of the breast fed.

The accompanying chart is particularly appropriate because this one case illustrates the three main points of discussion.

just as with whole cow's milk causes a definite shift in the findings toward those of the breast fed.

Whether the different stool reactions resulting from these carbohydrate additions are of any importance to the baby as a whole I do not know. I am simply calling them to your attention and hope by experiments now being conducted to learn more.

I also call to your attention that these studies were made with ordinary lactose. There is another brand recently put on the market called Beta-lactose, which has as its claim a somewhat sweeter and more soluble property than the other preparations. I have had no experience with this but hope to find time to check upon it in the near future.

You may wonder as to the significance of all this work. It has entirely changed my conception of the etiology of diarrhea occurring during nutritional disturbance of infants.

My scheme was formerly based on the following principles. A period of improper feeding leads to the development of nutritional disturbance. This in turn affects the digestive ferments. Under the changed intestinal conditions carbohydrates, especially lactose, ferment more readily. Acids of increased intensity are formed, irritate the intestine and lead to diarrhea.

Let us leave out the question of the primary or secondary importance of nutritional disturbance and consider the intestine.

We have learned that the stool of the breast fed is the most acid stool encountered. It is soft and frequently watery. In few diarrheas of the artificially fed have we met such acidity, unless the high acidity had already resulted from the proportions of the diet. In such cases the acidity had been maintained for weeks and was not the precipitating cause of the diarrhea. It looks to me as if the entire theory of excessive carbohydrate fermentation as a cause of diarrhea needs revision.

The larger stools in diarrhea on cow's milk suggest that this feeding demands more of the digestive secretions than does breast milk or else that its absorption into the body is not as perfect. An increased total excretion of neutralized acid in the

former, apparently closely correlated to the size of the stool, may result from increased acid formation. But as this acid is mostly bound or neutralized during its journey through the intestine the actual *degree* of acidity of the stool is low and the acidity itself cannot be a factor causing the diarrhea. Perhaps normally this same amount of acid is formed but is absorbed, while in the diarrhea it is swept out. Again maybe Moro was right and the location of the acid in the intestine is the important factor. At times it has seemed to me as if the body were adjusting its water balance and by discharging fluid from the tissues into the intestine was simply washing out the contents—the stools being an index of the conditions then existing in the intestinal tract. At any rate the idea of the danger of excessive acidity in these cases must be given up. All I can say at present is that if lactose is increased to a certain proportion, the stools begin to resemble those of the breast fed.

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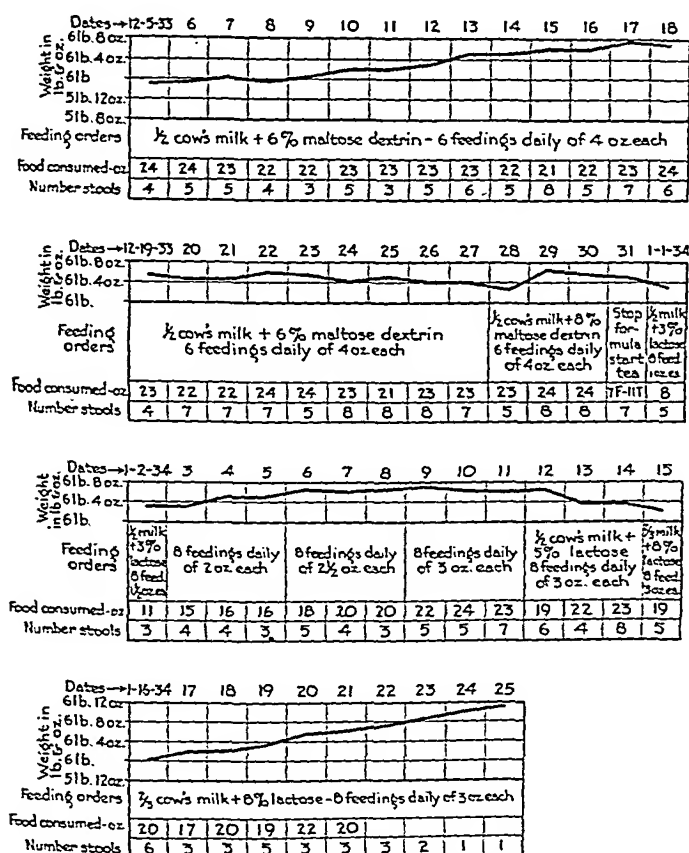


Fig. 280.—This figure illustrates in striking fashion three points raised in the discussion:

1. It supports Finkelstein's basic observation that some form of nutritional disturbance such as cessation of gain usually precedes diarrhea of this type.
2. It shows the importance of stressing clinical findings and interpretation of the weight curves as a guide to therapy above stool examination.
3. It demonstrates strikingly the fallacy of fearing carbohydrate *per se*.

Note: On January 22 to 25 inclusive, 24 ounces of food were consumed.

Baby H., a premature, weighing 4 pounds 8 ounces was admitted to my service when thirty-eight days old. He was given a mixture of one half cow's milk with 6 per cent maltose dextrin and in a month reached 6 pounds (beginning of chart). He gained slowly for the next two weeks and then began to lose. Stools increased in frequency and became watery and

green. Wishing to demonstrate the harmlessness of carbohydrate I increased it to 8 per cent. The result was a gain of several ounces followed by a loss and more diarrhea.

Not wishing to carry the experiment too far I reverted to orthodox treatment, substituting tea for several bottle feedings and then started small quantities of the bottle with low carbohydrate. Three per cent lactose was used in order to contrast this carbohydrate with the former. The quantity was increased slowly with no response of the weight curve and with no change in the character of the stools. Increase of lactose to 5 per cent led only to increasing diarrhea and loss of weight. Here was a dilemma. Should we follow orthodox indications, take away food and start over again—a rather dangerous procedure in so small a baby? Should we allow the liquid-green stools to guide the treatment?

Clinical examination showed the child not very sick. A study of the weight curve suggested a drop of weight that may be due to insufficient food. Certainly the drop is by no means precipitate enough at this time to suggest any of the severer disturbances as alimentary intoxication. A check on the formula shows the baby to be receiving insufficient calories for his age. Again it is thought that prematures require relatively more protein and mineral than full-term babies. Why not follow the indications suggested by the child than simply those of the gastro-intestinal tract? The formula was changed to two thirds milk with 8 per cent lactose. The weight curve responded, the diarrhea ceased and the baby is well.

Now as I said to you, I do not know whether it makes a particle of difference to the baby whether the stools are soft and acid like the breast fed or formed and alkaline like those of many receiving constipating mixtures. Looking at the baby first, it seems to me that children do equally well on either addition, lactose or maltose dextrin. However, I want to raise a question which has been perplexing me for some years. Is it merely a coincidence that nature has provided a food which gives certain intestinal reactions? Is the small, highly acid stool of the breast fed with its gram-positive flora simply an

accident of nature—or has nature designed a food the proportions of which are best adapted to the baby's general economy, to leave an acid intestinal residue? You see I am still thinking in terms of "baby first." I am thinking of the chemical composition of the food in relation to the baby's general metabolism. If nature has designed human milk which we agree to be the perfect food for the baby's body, and if the composition of this food leads to a certain type of stool, one may freely speculate as to whether the reverse is true. If it contained sufficient necessary essentials, would an artificial feeding leaving the same type of residue be best adapted to the baby's general health? This is merely material for reflection.

In the mean time I might call your attention to the work of Bergeim⁵ who some years ago maintained that in animal experiments lactose facilitated a better absorption of calcium and phosphorus from the intestine than did other carbohydrates. Here then is a tangible experiment which may aid us in solving some of the questions. Accordingly for the last three years I have been feeding infants dilutions of cow's milk with additions of similar amounts of either lactose or maltose-dextrin. We have been studying the intake of calcium and phosphorus in relation to their excretion in the urine and the stool. We have further controlled the work with studies of blood calcium and phosphorus, x-ray of the bones and clinical observations. This work is now being completed. Before many more months I hope to be able to present our results.

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fibers; from the latter, which lie beneath the endocardium of each ventricle, the impulse passes outward into the ventricular walls. The vagus nerve tends to diminish the heart rate, impeding the passage of stimuli from auricles to ventricles, while the sympathetic has the opposite effect.

When an impulse which arises at the *sino-auricular node* fails to pass the *auriculoventricular node* and bundle, it is said to be blocked and the term "heart block" is applied to the condition which results. Occurring most commonly at the *auriculoventricular junctional tissues*, this form is called *auriculoventricular heart block*; this may be classified as follows:

1. Partial block

- (a) delayed *auriculoventricular conduction*.

- (b) dropped beats; the ventricle no longer responds to every auricular beat but to every second, third or fourth beat.

2. Complete block or dissociation, when there is complete failure in conduction of impulses through the bundle.

Since in complete heart block the auricles cause no ventricular response, the ventricles initiate a rhythm of their own, from impulses originating in the common bundle (*His*) below the lesion; this new rhythm, known as *idioventricular*, is slow, regular, and possesses a rate of 35 to 30 beats per minute, or less. Occasionally it may be more rapid, 60 or more; the auricles on the other hand contract at their usual rate, at an entirely different rhythm from that of the ventricles. Accelerating or retarding influences such as fever, running or emotion which act on the sinus node have no effect on the *idioventricular* rhythm.

In the young, complete heart block is more often caused by either an acute general infection, such as *rheumatic fever*, *influenza*, *scarlet fever*; by trauma, or by congenital heart disease; in the elderly in whom complete block is more frequently found, the most frequent cause is *arteriosclerosis* of the coronary arteries supplying the junctional tissues, *infarction* of the septum, and less often *gumma* and tumor. That overactivity

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ILLINOIS

COMPLETE HEART BLOCK FOLLOWING INFLUENZA

It is generally conceded that, of the acute infections which cause heart block, rheumatic fever ranks first; that influenza also plays an important rôle is made manifest by the perusal of the recent literature which deals with the cardiovascular changes resulting from such an infection. Investigations by many observers have shown that not only the conduction system, but the entire circulatory system may suffer damage as a result of influenzal infection; these changes probably occur more frequently than generally supposed.

Mackenzie,¹ in his writings, states "it is possible that influenza may lay the beginning of a myocarditis, which ultimately leads to heart failure." Recently Hamburger² and others^{3, 4} have contributed to the literature on this problem.

The mechanism of heart block can best be understood by a study of the conduction system and by noting the nerve supply. Normally the excitation wave starts in a small area of specialized tissue at the junction of the superior vena cava with the right auricle, known as the sino-auricular node; in this node the plexuses of the vagus and sympathetic nerves, the inhibitors and accelerators of the heart terminate.

From this node, the impulse spreads over the auricles, causing auricular contraction and passes on to a second node, known as the auriculoventricular node, which lies in the lower part of the interauricular septum; here it is delayed. From the auriculoventricular node the impulse passes down the bundle of His, its two branches (one to each ventricle), and along their minute subdivisions constituting the Purkinje

block is usually associated with widespread myocardial disease, however, some degree of cardiac weakness is the rule.

REPORT OF A CASE

N. O., aged twenty-two years, white, male, was admitted to the hospital on the service of Dr. R. W. Keeton, on June 28, 1933, because of the following complaints: dyspnea on moderate exertion and pain of a vague character over the upper right abdominal quadrant; these had been present for about four months. He had not been taking digitalis.

In November, 1932, eight months prior to his first hospital admission, he contracted an acute influenzal infection, which was followed by a slow convalescence; a syncopal attack occurred the following February and it was at this time that the slow pulse was discovered.

As a child, he had two operations for mastoid infection; at the age of eighteen years, an operation for strabismus was performed at the Cook County Hospital; an examination of the hospital record revealed a pulse rate of 72, no cardiac enlargement and a normal blood pressure; at the age of twenty years he passed a physical examination for life insurance. The family history is irrelevant.

Physical examination: The patient did not appear ill or distressed, there was no fever, nor were there signs of congestive heart failure. Inspection of the jugular bulbs revealed clearly regular venous pulsations approximately three times as rapid as the ventricular rate at the apex; the pulses were equal, regular and of good force.

The heart showed definite enlargement, the apex impulse being in the fifth interspace, $11\frac{1}{2}$ cm. to the left of the mid-sternum; no increase in supracardiac dulness; a short soft systolic murmur was audible at the apex. The rhythm was regular, 31 to the minute; in the long intervals between the ventricular systoles, muffled auricular sounds could be heard, causing at times a marked accentuation of the first ventricular sound; the second aortic sound was accentuated; the systolic blood pressure was 190 and the diastolic 70 mm. Hg.

of the vagus or the administration of digitalis in large doses is capable of producing complete heart block is denied by some.

Complete heart block may be present without symptoms; syncope is not a constant finding due to the fact that the ventricles initiate their own rhythm. The blood pressure is unaffected unless the ventricular rate is very slow when the systolic pressure rises while the diastolic remains unchanged, resulting in an elevation of the pulse pressure; it is stated that this striking change in the blood pressure has been observed to occur in persons with heart block in whom there is evidence of peripheral arteriosclerosis.

The clinical recognition of complete heart block affords no difficulty in most instances; certain cases however can only be recognized by means of the electrocardiogram. The slow ventricular rate is very suggestive of complete block, but not conclusive; however by noting the venous pulsations in the neck and observing the difference in rate as compared with the rate at the apex or at the wrist, the diagnosis may be made. When muffled sounds are heard on auscultation over the precordium, separated from the sounds of the ventricular beats, complete heart block should be diagnosed; at times these sounds may coincide with the ventricular contraction causing accentuation of either the first or second sound.

Adams-Stokes' syndrome forms the chief complication but does not occur very frequently. The mechanism underlying this syndrome is either a slowing or standstill of the ventricles, or a marked ventricular tachycardia often ending in fibrillation.

The prognosis in complete heart block may be said to depend not so much on the presence of the block as upon the myocardial integrity. The presence of Adams-Stokes' syndrome adds to the gravity of the prognosis; older people with complete heart block have a poor prognosis because of the considerable myocardial damage usually present.

Sprague and White⁵ have recently called attention to the fact that heart block may be borne for years without seriously affecting the health of the individual. Harris states that complete heart block is compatible with normal life. Since heart

The patient left the hospital and returned for readmission on October 27, 1933. An electrocardiogram taken at this time was practically the same as the one taken previously. It was then deemed advisable to try the use of thyroid extract. Blackford and Willius⁶ reported favorably on the use of thyroxin in cases of complete heart block with Adams-Stokes' syndrome. Our patient received, orally, 3 grains thyroid extract per day, taking 26 grains in all; at the end of this period an electrocardiogram was taken (Fig. 281, B); no change from the previous tracing was discernible. According to Willius, the benefit derived from thyroid administration, is due to an increased circulation rate, and a consequent improved blood supply.

He was next given barium chloride, $\frac{1}{2}$ grain, three times a day for fourteen days. Strauss and Meyer⁷ report good results from barium in preventing Adams-Stokes' attacks while Herrmann and Ashmann⁸ obtained a favorable result in a case of transient complete heart block; in our case barium chloride was ineffective. The basis for the use of barium chloride depends on its ability to keep the idioventricular pacemaker in an irritable state, thus preventing ventricular standstill.

Adrenalin is frequently reported in the literature as being of benefit in cases of complete heart block, whether or not Adams-Stokes' syndrome is present. The normal response of a subcutaneous injection of adrenalin in therapeutic doses of 0.5 to 1 cc. of a 1/1000 solution, usually consists of an acceleration of both the auricular and ventricular rates, an increase of the systolic and at times a lowering of the diastolic blood pressure, resulting in an increase of pulse pressure; adrenalin also produces ventricular extrasystoles. The action is due to stimulation of the sympathetic nerve endings in the cardiac muscle.

On the other hand, if the vagal tone is good, the administration of adrenalin may result in a slowing of the ventricular rate by stimulating the vagal inhibitory center.

Adrenalin is also thought by some to be capable of dilating the coronary arteries.

In the presence of hypertension, the response to adrenalin is a sudden and intense increase of the systolic blood pressure;

The liver and spleen were not palpable; basal metabolism was within normal limits; the urine was normal, Wassermann reaction negative; there was no edema.

A teleroentgenogram of the chest showed the lungs to be negative, the heart enlarged to the left.

x-Rays of the gallbladder and gastro-intestinal tract proved negative. An electrocardiogram (Fig. 281, A), taken on day

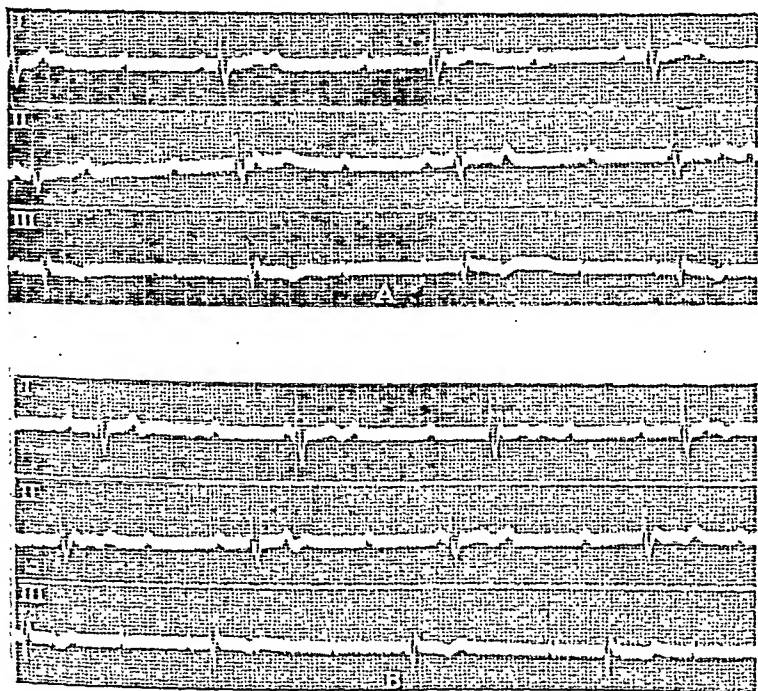


Fig. 281.—A, Electrocardiogram taken on day of admission. Auricular rate 94, ventricular rate 31. B, After oral administration of 26 grains of thyroid extract.

of admission, shows complete heart block, with slurring of QRS. complex in lead I, and splintering in the remaining leads; left axis deviation. Auricular rate 94, ventricular rate 31.

Atropine had no effect on the block; neither was any change noticeable after digitalis.

jection of 1 cc. of a 1/1000 solution of adrenalin chloride in the case being reported, electrocardiograms recorded during this period are as follows: Five minutes after the injection of adrenalin, the electrocardiogram* (Fig. 282, A) showed an auricular rate of 115, and a ventricular rate of 40. After ten minutes, another electrocardiogram was taken (Fig. 282, B, C, D), and shows the auricular rate reduced to 88, while the ven-

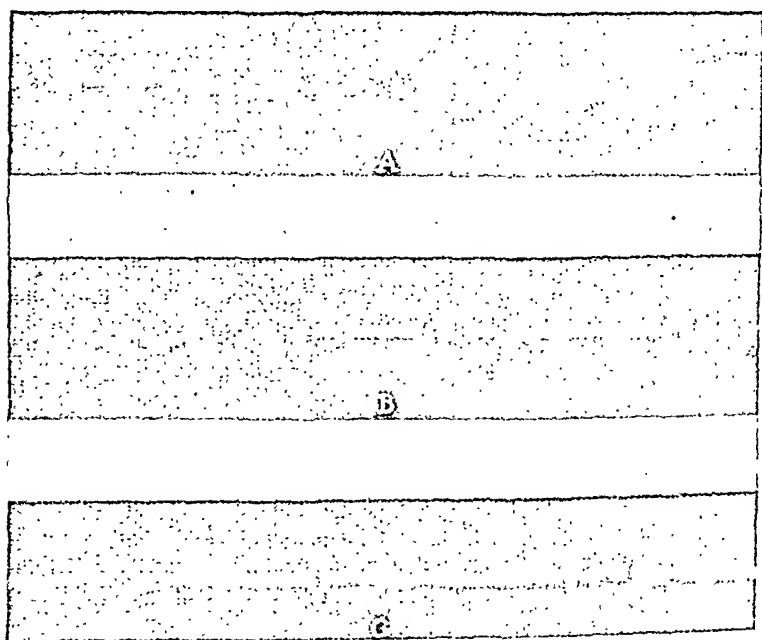


Fig. 283.—A and B, Twenty minutes following subcutaneous injection of adrenalin; A represents the period during which the patient fainted; C, auricular rate 114, ventricular rate 37 (see text).

tricular rate increased to between 94 and 107. There is nodal rhythm with marked arborization, first in one branch, then in another; this is followed by a complete bundle branch block, tending to return within this five-minute period to the original type of complex; numerous ventricular extrasystoles are also shown; a block in the other branch of the bundle follows.

* All tracings in Figs. 282 and 283 are of lead I.

After fifteen minutes the tracing (Fig. 282, E) assumes its original character.

In twenty minutes the patient fainted momentarily. The electrocardiogram, taken during this interval (Fig. 283, A), shows the following: numerous ventricular extrasystoles arising in various foci, finally becoming rapid and showing a few beats resembling a ventricular fibrillation; following this the tracing (Fig. 283, B) shows numerous ventricular extrasystoles, at times appearing in paroxysms of five extrasystoles, arising in both the right and left ventricles. This continues for some time until finally a pulsus bigeminus (Fig. 283, C) is shown with every other beat an extrasystole. The auricular rate is 114 and the ventricular rate 37.

Fortunately the patient revived spontaneously and after a brief rest was able to walk to his bed. At present he is quite comfortable.

Adrenalin should not be used indiscriminately in treating patients with complete heart block who are subject to syncopal attacks without a definite knowledge of the mechanism underlying these seizures. Where syncope results from a marked slowing or standstill of the ventricle the use of adrenalin in a 1/1000 solution is indicated and may be a life-saving drug. It is contraindicated on the other hand in those cases in whom a ventricular fibrillation is at the bottom of the syncope.

Summary and Conclusions.—A case of influenza complicated by complete heart block is reported.

Influenza plays an important rôle in the production of serious damage to the cardiovascular system.

Following the subcutaneous injection of 1 cc. of a 1/1000 adrenalin chloride solution a syncopal attack was induced.

Caution in the use of adrenalin is urged.

Electrocardiograms are presented showing the patient's normal tracing, after thyroid medication, as well as the successive electrocardiograms following the subcutaneous injection of adrenalin.

Note.—I wish to express my appreciation to Dr. R. W. Keeton for kind suggestions and advice; to Dr. Sidney Strauss

for interpreting the electrocardiograms, and to Dr. F. H. Hick for permission to present this patient. I am especially indebted to Miss Marion Hood for technical assistance and painstaking preparation of the electrocardiograms.

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CLINIC OF DR. CLIFFORD J. BARBORKA

PASSAVANT MEMORIAL HOSPITAL

DIET IN THE MANAGEMENT OF NEPHROSIS

THE word nephrosis was introduced in 1905 by Freidrich von Muller to express degenerative changes in the kidney in contrast to the inflammatory and proliferative changes of nephritis. About ten years later Munk, Volhard, Farr and Govaerts began applying the term clinically. Epstein, who champions the view that this entity is indicative of a profound metabolic disturbance in which there is poor utilization of protein, feels that it is not primarily a disease of the kidneys, and he advocates a very high protein diet. Other terms have been applied such as lipoid nephrosis.

From the standpoint of the pathologist it may be helpful to use the term nephrosis for degenerative lesions, but from the clinical standpoint we cannot as yet prophesy whether the pathologist will find, as stated by Christian, "more or less nephrosis or less or more nephritis." For example, patients who in the earlier stages might be regarded as having true nephrosis, may end in death with the finding of a chronic glomerulonephritis. In Bannick's recent report on lipoid nephrosis and its reaction to glomerulonephritis he has suggested that lipoid nephrosis and the so-called "nephrotic syndrome," in adults at least, is a form of Bright's disease. The question of using the term as a disease entity or rather the name of a syndrome which may occur in the many forms of acute, sub-acute, or chronic nephritis is open to research and the future to determine.

The outstanding clinical findings of nephrosis are: Edema with marked albuminuria; during edematous stage small amount of urine; as edema lessens urine volume increases; decrease in blood proteins with relative increase in globulin, and decreased albumin reversing the usual albumin to globulin ratio; presence of double refracted lipoid droplets in the urine; increase in blood lipoids; decreased basal metabolism often as low as minus 30 to minus 40. With these findings there is an absence of the usual signs of nephritis, such as hematuria, increased nonprotein nitrogen, urea, uric acid or creatine in the blood, impaired excretion of phthalein and high blood pressure.

Barker and Kirk, working in Christian's Clinic, have been able to show experimentally facts which suggest that in nephrosis the clinical features result primarily from the protein loss consequent to a marked albuminuria and that the edema is perhaps due to physiochemical changes incident to the continued loss of blood protein. Fishberg at Beth Israel Hospital, New York, has shown the development of lipoidemia as a compensatory phenomenon for protein decrease.

Whatever the true nature of nephrosis may be, we may summarize by stating that the presence of nephrosis does not mean that a definite and isolated form of pathologic lesion will be found in the kidney, but there may be degenerative lesions of the tubules with normal appearing glomeruli, or there may be inflammatory and proliferative glomerular lesions that will progress into typical chronic glomerular nephritis. Further, all these lesions may be found by the pathologist and yet the patient may never have manifested signs of nephrosis clinically.

The important practical contribution from the studies of nephrosis is in reference to the protein loss and the emphasis of the need of giving a liberal amount of protein to replace the loss of albumin in cases of edema when the phthalein output is good and there is no increase in blood urea or other evidence of renal incompetency.

While exceedingly high protein diets, such as 200 to 250 Gm. a day, may be impossible for many patients to take day in and

day out, a high protein intake of from 80 to 150 Gm. is ordinarily tolerated and will accomplish wonderful results. Certainly in all cases presenting the nephrosis syndrome with no nitrogen retention in the blood, a diet rich in protein should be given a trial.

The important factors in the dietary treatment of nephrosis are:

1. High protein content.
2. Low fluid intake.
3. Low salt.
4. Low fat content.
5. High carbohydrate content.

The chief difference in the diet prescribed for nephrosis and chronic nephritis with edema is the greater emphasis on a high protein intake and lower fat content. The reason for this difference is the belief that in a large part the edema of nephrosis is the result of a low blood protein content. One should be very cautious in the use of high protein diets when there is nitrogen retention in the blood.

The fluid intake must be limited to an amount that will approximately balance the output of the kidney without the influence of diuretics. When diuretics are used the fluid intake should be restricted, regardless of the output as influenced by the diuretics.

The salt content of the diet should be kept low. A diet is considered low in salt if only a sparing amount of salt is used in the preparation of food and no extra salt or other condiments are used at the table or when the food is served. A normal amount of salt is allowed in the bread and butter. Such a diet contains approximately 2 to 4 Gm. of salt daily. In some cases of chronic nephrosis it may be desirable or necessary to place the patient upon a salt-free diet. A salt-free diet is one in which all food is prepared without salt, even the bread and butter being salt free and no salt or other condiments are added at the table. Such a diet contains approximately 0.5 Gm. of salt daily.

One of the chief difficulties in administering the salt-free

diet is, many times, a loss of appetite, due to the lack of taste and its influence on the flavor of foods. A large number of salt substitutes are on the market; few of them are of distinct value. Potassium chloride and potassium nitrate may be used as a salt substitute. These have the added advantage of acting as a diuretic. One may give 3 to 5 Gm. a day.

In nephrosis the blood plasma being low in protein and high in lipid content it is necessary that the diet be low in fat in order that a more economical use of protein may be permitted.

The carbohydrate content should be high primarily because its protein-sparing properties are more efficient than fat. In cases where there is a tendency to nausea it is more likely to be better tolerated than fat.

DIRECTIONS FOR APPLICATION OF DIETS

In order to teach the application of the quantitative and estimated quantitative total food allowance for one day we have found in our experience that the best plan is to divide this food into three meals. This will insure a better understanding especially on the part of the patient, of the proper distribution of the total amount of food required in the diet. We have therefore, outlined, on the opposite page of each quantitative and estimated quantitative diet presented, a suggested distribution of the total food allowance for one day into three meal expressed first in household measures and then their equivalent in gram weight. These are not menus but skeleton outline which simplify the planning of the day's menu and allow for variation of foods from day to day.

With the above factors in mind three high protein diets for cases with nephrosis are presented, one containing 80 Gm. of protein with 2000 calories, the second containing 100 Gm. of protein with 2200 calories and the last containing 150 Gm. of protein with 2600 calories. The diets may be made either salt free or low salt as the case necessitates, depending upon the edema present.

The selection of the amount of protein or calories will de

pend upon the ideal weight and the individual needs of the case at hand.

The protein content of any of the diets may be increased or decreased by the addition or subtraction of protein foods. For example, one egg furnished 6 Gm. of protein and 6 Gm. of fat; 20 Gm., or a 1-inch cube, of solid cheese furnishes 6 Gm. of protein and 7 Gm. of fat; 45 Gm. of meat, or 1½ ounces, furnishes 11 Gm. of protein and 7 Gm. of fat.

The caloric content in this series may be increased or decreased, without having any essential bearing on the protein content by adding to or subtracting from the diet a part of the carbohydrate or fat or both. For example:

1. One teaspoon (5 Gm.) sugar or jelly or jam is approximately 20 calories.

2. One glass 10 per cent fruit juice is approximately 80 calories.

3. One square (10 Gm.) of butter is approximately 75 calories.

4. One tablespoon (15 Gm.) salad dressing made with oil is about 115 calories.

The approximate average water and mineral content, expressed in grams, of the diets are:

Water.....	1220
Sodium.....	0.804
Potassium.....	3.808
Calcium.....	0.541
Magnesium.....	0.308
Chloride.....	0.861
Phosphorus.....	0.454
Sulphur.....	1.263
Iron.....	0.0211

NEPHROSIS

80 Grams Protein

2000 Calories

Quantitative and Estimated Quantitative
Total Food Allowance for One Day

Carbohydrate 285, Protein 80, Fat 60, Calories 2000

Food.	Gram weight.	Household measure.
Cereal (cooked).....	140	$\frac{2}{3}$ cup
Bread.....	90	3 slices
Butter.....	20	2 squares
Salad dressing with oil.....		
Milk (skimmed).....	100	$\frac{1}{2}$ glass
Cream, 20 per cent.....		
Cream, 40 per cent.....		
Meat (lean).....	180	2 large servings (6 ounces)
Bacon.....		
Eggs.....	100	2 eggs
Vegetables, 3 per cent } Vegetables, 6 per cent }	300	3 servings (1 $\frac{1}{2}$ cups)
Fruit, 10 per cent } Fruit, 15 per cent }	400	4 servings
Potato or substitute.....	200	2 servings (1 cup)
Sugar.....	30	2 tablespoonfuls
Jelly or jam.....	105	$\frac{1}{2}$ cup (7 tablespoonfuls)

NEPHROSIS

80 Grams Protein

2000 Calories

Suggested Distribution of Total Food
Allowance for One Day*Breakfast*

		Gm.
Fruit.....	1 serving	(100)
Cereal (cooked).....	$\frac{2}{3}$ cup	(140)
Eggs.....	2 eggs	(100)
Bread (toast).....	1 slice	(30)
Butter.....	$\frac{1}{2}$ square	(5)
Sugar.....	2 tablespoonfuls	(30)
Jelly or jam.....	2 tablespoonfuls	(30)
Milk (skimmed).....	$\frac{1}{2}$ glass	(100)

Luncheon

Meat.....	1 large serving	(90)
Potato or substitute.....	1 serving	(100)
Vegetables, 3 or 6 per cent.....	2 servings	(200)
Bread.....	1 slice	(30)
Butter.....	$\frac{1}{2}$ square	(5)
Fruit.....	1 serving	(100)
Jelly or jam.....	3 tablespoonfuls	(45)

Dinner

Meat.....	1 large serving	(90)
Potato or substitute.....	1 serving	(100)
Vegetable, 3 per cent.....	1 serving	(100)
Fruit salad.....	1 serving	(100)
Bread.....	1 slice	(30)
Butter.....	1 square	(10)
Fruit.....	1 serving	(100)
Jelly or jam.....	2 tablespoonfuls	(30)

NEPHROSIS

100 Grams Protein

2200 Calories

Quantitative and Estimated Quantitative
Total Food Allowance for One Day

Carbohydrate 290, Protein 100, Fat 70, Calories 2190

Food.	Gram weight.	Household measure.
Cereal (cooked).....	140	$\frac{2}{3}$ cup
Bread.....	90	3 slices
Butter.....	.20	2 squares
Salad dressing with oil.....		
Milk (skimmed).....	100	$\frac{1}{2}$ glass
Cream, 20 per cent.....		
Cream, 40 per cent.....		
Meat (lean).....	225	2 very large servings (8 $\frac{1}{2}$ ounces)
Bacon.....		
Eggs.....	100	2 eggs
Vegetables, 3 per cent } Vegetables, 6 per cent }	300	3 servings
Fruit, 10 per cent } Fruit, 15 per cent }	400	4 servings
Potato or substitute.....	200	2 servings
Sugar.....	15	1 tablespoonful
Jelly or jam.....	90	6 tablespoonfuls
Candy.....	40	4 to 5 small pieces

NEPHROSIS

80 Grams Protein
2000 Calories

Suggested Distribution of Total Food
Allowance for One Day

Breakfast

		Gm.
Fruit.....	1 serving	(100)
Cereal (cooked).....	$\frac{2}{3}$ cup	(140)
Eggs.....	2 eggs	(100)
Bread (toast).....	1 slice	(30)
Butter.....	$\frac{1}{2}$ square	(5)
Sugar.....	2 tablespoonfuls	(30)
Jelly or jam.....	2 tablespoonfuls	(30)
Milk (skimmed).....	$\frac{1}{2}$ glass	(100)

Luncheon

Meat.....	1 large serving	(90)
Potato or substitute.....	1 serving	(100)
Vegetables, 3 or 6 per cent.....	2 servings	(200)
Bread.....	1 slice	(30)
Butter.....	$\frac{1}{2}$ square	(5)
Fruit.....	1 serving	(100)
Jelly or jam.....	3 tablespoonfuls	(45)

Dinner

Meat.....	1 large serving	(90)
Potato or substitute.....	1 serving	(100)
Vegetable, 3 per cent.....	1 serving	(100)
Fruit salad.....	1 serving	(100)
Bread.....	1 slice	(30)
Butter.....	1 square	(10)
Fruit.....	1 serving	(100)
Jelly or jam.....	2 tablespoonfuls	(30)

NEPHROSIS

150 Grams Protein

2600 Calories

Quantitative and Estimated Quantitative
Total Food Allowance for One Day

Carbohydrate 310, Protein 150, Fat 85, Calories 2605

<i>Food.</i>	<i>Gram weight.</i>	<i>Household measures.</i>
Cereal (cooked).....	140	$\frac{2}{3}$ cup
Bread.....	90	3 slices
Butter.....		
Salad dressing with oil.....		
Milk (skimmed).....	100	$\frac{1}{2}$ glass
Cream, 20 per cent.....		
Cream, 40 per cent.....		
Meat (lean).....	450	2 very large servings (15 ounces)
Bacon.....		
Eggs.....	100	2 eggs
Vegetables, 3 per cent } Vegetables, 6 per cent }	300	3 servings
Fruit, 10 per cent } Fruit, 15 per cent }	400	4 servings
Potato or substitute.....	200	2 servings
Sugar.....	30	2 tablespoonfuls
Jelly or jam.....	135	9 tablespoonfuls

NEPHROSIS

100 Grams Protein

2200 Calories

Suggested Distribution of Total Food

Allowance for One Day

Breakfast

		Gm.
Fruit.....	1 serving	(100)
Cereal (cooked).....	$\frac{2}{3}$ cup	(140)
Eggs.....	2	(100)
Bread (toast).....	1 slice	(30)
Butter.....	$\frac{1}{2}$ square	(5)
Sugar.....	1 tablespoonful	(15)
Jelly or jam.....	2 tablespoonfuls	(30)
Milk (skimmed).....	$\frac{1}{2}$ glass	(100)

Luncheon

Meat.....	1 very large serving	(120)
Potato or substitute.....	1 serving	(100)
Vegetables, 3 or 6 per cent.....	2 servings	(200)
Bread.....	1 slice	(30)
Butter.....	$\frac{1}{2}$ square	(5)
Jelly or jam.....	2 tablespoonfuls	(30)
Fruit.....	1 serving	(100)
3.00 p. m. Candy.....	4 to 5 small pieces	(40)

Dinner

Meat.....	1 very large serving	(135)
Potato or substitute.....	1 serving	(100)
Vegetable, 3 per cent.....	1 serving	(100)
Fruit salad.....	1 serving	(100)
Bread.....	1 slice	(30)
Butter.....	1 square	(10)
Jelly or jam.....	2 tablespoonfuls	(30)
Fruit.....	1 serving	(100)

A Few Suggested Substitutions

1. In the place of one slice of *bread* may have one of the following:
 1. Potato—one small serving (75 Gm.).
 2. Macaroni—one small serving (75 Gm.).
 3. Cereal—one small serving (140 Gm., cooked).
2. In the place of *one egg* may have one of the following:
 1. Meat, chicken or fish—one very small serving (1 ounce).
 2. Solid cheese—one 1-inch cube.
 3. Cottage cheese—2 tablespoonfuls.
 4. Milk—1 glass.
3. In the place of *one tablespoon of salad dressing made with oil* may have one of the following:
 1. $1\frac{1}{2}$ squares of butter.
 2. $1\frac{1}{2}$ glass of 10 per cent fruit juice.
 3. 3 small pieces of candy.
 4. 2 tablespoonfuls jelly or jam.
 5. 2 tablespoonfuls sugar.

CONCLUSIONS

A brief review of nephrosis with emphasis upon the important factors in the dietary management has been presented.

The detailed outline of diets will aid the physician in instructing and applying the proper diet therapy in the treatment of nephrosis, especially in patients who cannot avail themselves of hospitalization or the aid of a competent dietitian.

Acknowledgment is made to my consulting dietitian, Miss Pearl Lewis, for her work in calculating the diets presented in this clinic.

NEPHROSIS

150 Grams Protein

2600 Calories

Suggested Distribution of Total Food
Allowance for One Day*Breakfast*

		Gm.
Fruit.....	1 serving	(100)
Cereal (cooked).....	$\frac{2}{3}$ cup	(140)
Eggs.....	2 eggs	(100)
Bread (toast).....	1 slice	(30)
Sugar.....	2 tablespoonfuls	(30)
Jelly or jam.....	3 tablespoonfuls	(45)
Milk (skimmed).....	$\frac{1}{2}$ glass	(100)

Lunch

Meat.....	1 extra large serving	(225)
Potato or substitute.....	1 serving	(100)
Vegetable.....	2 servings	(200)
Bread.....	1 slice	(30)
Jelly or jam.....	3 tablespoonfuls	(45)
Fruit.....	1 serving	(100)

Dinner

Meat.....	1 extra large serving	(225)
Potato or substitute.....	1 serving	(100)
Vegetable.....	1 serving	(100)
Fruit salad.....	1 serving	(100)
Bread.....	1 slice	(30)
Jelly or jam.....	3 tablespoonfuls	(45)
Fruit.....	1 serving	(100)

SUBSTITUTIONS

The following substitutions have been planned so that the protein, calories, minerals and vitamin content are not appreciably changed.

The carbohydrate and fat content varies proportionately to the amount of fat substituted for pure carbohydrates or the amount of pure carbohydrate substituted for fats, as 1 tablespoonful salad dressing with oil contains approximately no carbohydrate, 13 Gm. fat and 120 calories, while 2 tablespoonfuls sugar contain approximately 30 Gm. carbohydrate, no fat and 120 calories.

other physical findings were negative except for a chronic endocervicitis. Cystoscopic examination revealed only a slight hyperemic condition of the bladder. Wassermann and Kahn were negative; red blood cells 4,310,000, white blood cells 7480, hemoglobin 87 per cent. Differential smear polymorphonuclear cells 63 per cent, lymphocytes 30, mononuclears 5 per cent. Urine negative except for occasional white blood cell. On January 21, 1929, she complained of a sore mouth and increased malaise. The sore throat and mouth became more painful in the succeeding two days and examination showed only an infection of the gum margins resembling a beginning pyorrhea. On January 24th the temperature was 103.2° F. and there was constant soreness and burning sensation in the vagina. There were areas of faint injection over the roof of mouth and buccal mucous membranes and lower outer gums where minute amounts of white flaky material resembling thrush were found. The white blood cell count was 800 with no polymorphonuclear cells. She was given x-ray therapy, 27 R. units dose over the long bones and pelvis on January 26th and January 28th. The leukocytes gradually rose to a total of 28,400 on February 1st and 67 per cent polymorphonuclear cells. The blood count remained high for three days and then dropped to 8000 with 57 per cent polymorphonuclears. She developed an upper respiratory infection and the leukocyte count fell to 2000 and an absence of polymorphonuclears. Liver Extract Lilly No. 343, 6 vials daily for ten days, was given without improving the blood count. The x-ray treatment was given the second time in the same dosage as used previously to no avail. Two blood transfusions were given on March 1st and March 3rd with no improvement in the white cell count which averaged 200 per cubic millimeter, counted in triple concentration, with total absence of polymorphonuclears. Patient died on March 10, 1929, with extensive mouth, throat, vaginal and rectal ulcerations. The anatomical diagnosis at necropsy was gangrenous ulceration of the base of the tongue, and the mucous membranes of the epiglottis and pyriform fossa. Gangrenous ulceration of the right border of the mouth. Gangrenous ulceration of the rectum,

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NEUTROPENIA, "AGRANULOCYTIC ANGINA," REPORT OF CASES AND TREATMENT

SINCE the publication of the observations by Schultz¹ in 1922, dealing with the signs and symptoms of "agranulocytic angina," there have appeared numerous contributions on the etiology, behavior and treatment of this disease. It is now quite generally accepted that Schultz described only one form of neutropenia which was very malignant and probably represents a definite clinical entity. Since then it has been shown that the disease may occur in an acute or chronic form and may be either very malignant or benign. It is a disease of unknown etiology. The characteristic blood picture is one of a leukopenia associated with a marked reduction in the granular white blood cells. Examination of the myeloid tissue shows it to be hyperplastic, aplastic or even normal in appearance. As is always true in a disease with a high mortality rate, a large number of therapeutic agents and measures have been tried with only questionable success. None of these offer any apparent sustaining effect. The two cases presented in this report, one an acute primary malignant form and the other a benign primary neutropenia, illustrate the findings usually associated with each group and the treatment that is commonly used.

Case I.—Female, age twenty-seven, housewife, was first admitted to the Billings Memorial Hospital in August, 1928, complaining of burning sensation on urination. In the course of the physical examination she was found to have an active pulmonary tuberculosis and sent to a sanatorium for care. All

Case II.—A female tissue technician, single, age twenty-eight, admitted to the Billings Memorial Hospital Out-patient Clinic on November 5, 1931. The chief complaints were general malaise, muscular fatigue, loss of appetite and recurring sore throats. Her past history was significant, having had the sore throats since the age of fourteen, occurring four or five times each winter with more than average severity. She had an attack of acute rheumatic fever at the age of nineteen and severe attacks of influenza in 1918, 1928 and 1931.

At the age of twenty, in 1924, she was admitted and diagnosed at the Mayo Clinic as appendicitis. The blood findings at that time were all within normal limits. It is interesting to note that in 1929, at the age of twenty-four, while studying in a technician's course, she made a white blood cell count on herself and it was found to be 4500. Repeated counts at the time showed it to be the same. Coincident with this finding she first noted the appearance of the symptoms of fatigue and malaise which have persisted up until the present time. The intervals of well being have gradually decreased.

Physical examination revealed a well-developed and nourished female about the stated age. She was not acutely ill, but appeared tired. Temperature of 99.4° F. Throat slightly injected, but no ulcerations were apparent. Otherwise the general physical examination was normal. The Wassermann and Kahn tests on the blood were negative. Red blood cells 4,550,000, hemoglobin 85 per cent (Dare), platelet count 320,000, white blood count 5200. Differential blood smear, polymorphonuclears 4 per cent, large lymphocytes 21 per cent, small lymphocytes 68 per cent, mononuclears 7 per cent. There were no immature cells seen and the red cells showed no abnormalities. Bleeding and coagulation time normal. Urine negative. Blood culture negative. Agglutination for *Bacillus melitensis* was negative. The urea clearance test showed presumably normal kidney function. Nonprotein nitrogen was 34 mg./100 cc. Basal metabolic rate was -13 per cent. x-Ray of the chest showed no pulmonary pathology. Since the patient had been working as a bone technician and was accus-

cecum and vaginal walls. Multiple areas of necrosis in the lungs. Slight hyperplasia of the spleen. Beginning bronchopneumonia. Fibrocaceous tuberculosis of the apex of the right lung, hypoplasia of the bone marrow. Histology of the sections revealed: Lymph nodes, marked hyperplasia of the endothelial cells of the sinuses with little phagocytosis and absence of leukocytes. Spleen, marked hyperplasia of the endothelial cells in the pulp with reduction of lymphoid elements. Bone marrow shows little active tissue and in the active areas are only very few polymorphonuclear cells. Few megalokaryocytes are present. All ulcerated areas are gangrenous with large bacterial masses. The tissue surrounding the necrotic areas show infiltration with round cells resembling immature lymphocytes.

This case illustrates the clinical picture, the symptoms and laboratory findings that are commonly found in cases of malignant neutropenia. Necropsy showed practically no active myeloid tissue. Examination of the patient both during the course of the illness and at postmortem revealed no etiologic basis for her condition. Of particular interest in this case were three therapeutic measures employed: Liver extract, blood transfusions and x-rays over the long bones, ribs and pelvis. Liver extract and blood transfusions had no effect on the blood picture. x-Ray was administered over the long bones and the pelvis for two days at a time when there were no granular cells and total white blood cell count was 800. The dosage used was 27 roentgen units. On the second day after x-ray therapy the count had risen to 28,400 total leukocytes with 57 per cent polymorphonuclears. It is interesting to note that subsequent use of the x-ray, even in larger doses, failed to alter the blood picture. This fact agrees with the findings of Doan² and others who believe that with an aplastic bone marrow the effect of the x-ray is to call forth all the reserve cells and deplete the granulopoietic tissue. The interpretation, then, that an increased number of white blood cells in the peripheral blood stream represents a beneficial effect of x-ray therapy is unwarranted. In reality it probably hastens the fatal outcome.

the leukocyte count was 2600 and there were no polymorphonuclear cells. On March 2, 1933, there was a marked increase in the degree of fatigue. Daily blood counts for the following eleven days revealed the polymorphonuclear cells ranging between 2 per cent and 8 per cent with an average leukocytic count of 2000 cells. Sodium nucleinate was used the second time, followed by a rise in the leukocytic count. She developed a sore throat on March 13th and the count immediately started to rise. By March 23rd the throat had entirely cleared up. She felt well and the white blood cell count was 3500 with 12 per cent polymorphonuclear cells. However, by April 3, 1933, she again had ulcerations in the mouth, could speak with difficulty because of an edematous tongue and there were 2 per cent granulocytes with a total leukocytic count of 2000. A vital stain of the contents of a small buccal abscess revealed 3 living and 17 nonstaining polymorphonuclear cells, 33 lymphocytes and 38 mononuclears. Daily blood smears until April 8th, five days later, showed 2 per cent polymorphonuclears to be the maximum percentage. At this time nuclein intramuscularly, 1 cc. daily, was administered for ten days. The count started to rise on the fourth day and a maximum of 5300 white blood cells and 25 per cent polymorphonuclear cells was attained on the eighteenth day after this particular treatment was initiated. On May 1st there was a relapse, the white blood cell count was 2100 and no polymorphonuclear cells were seen. The nuclein intramuscular therapy was repeated for three days without objective evidence of clinical relief. It was discontinued at request of patient. There was an almost imperceptible rise in the total number of white blood cells. Even during the course of the therapy, she developed a large ulcer on the tongue, which became very inflamed on the fourth day and with the appearance of inflammation it started to clear up. There was an accompanying rise in the white blood cellular elements. The count after this infection reached a maximum of 5000 white blood cells and 38 per cent polymorphonuclears. In view of the fact that benzene or its product was still considered as a possible etiologic agent, she was advised to leave the labora-

tomed to handling large amounts of xylol and benzol, twenty-four-hour urine samples were analyzed and failed to show any traces of these products. This patient was followed very closely for one year, during which time there was little change in the clinical picture. Easy fatigue and frequent mild sore throats were the chief findings. She ran a continuous low-grade fever varying between 99° and 100° F. A tonsillectomy was done on December 11, 1931, without altering either patient's condition or the blood picture. On October 25, 1932, she was admitted to hospital complaining of headaches, sore throat and extreme prostration. The pharynx was injected. There were superficial ulcerations at the gingival margins, and the gums were oozing blood. The white blood cell count was 1800 and there were no granulocytes. On the 26th she was given intramuscularly 0.7 Gm. of pentose nucleotide K-96, being repeated daily for ten days. There was a leukocytic rise on the second day which gradually reached a maximum on the ninth day, cell of 6700, granulocytes 32 per cent, lymphocytes 64 per cent and monocytes 4 per cent. On January 9, 1933, she was readmitted to the hospital with an interim history of malaise, occasional mild sore throat and a low-grade temperature. There was an abrasion on the left small toe which was swollen and red. The redness extended in streaks well above the knee. This infection in the toe was associated with real chills and fever. The total leukocytic count was 2750 and there were no granulocytes in the peripheral blood stream. Only treatment instituted on this occasion was hot saline dressings to the left foot and leg. The infection rapidly cleared and the white blood cell count was 4700 with 48 per cent polymorphonuclear neutrophils. Patient felt well until she had a relapse on February 10, 1933, accompanied by a severe sore throat and bleeding gums. The total leukocytic count was 2000 and there were only 4 per cent polymorphonuclear cells. She was placed on sodium nucleinate by mouth 4 Gm. per day for ten days. On the third day the count was 3600 leukocytes and 28 per cent neutrophils. After reaching this peak the count immediately started a gradual decline. On February 27, 1933,

a marked leukopenia with a total disappearance of polymorphonuclear cells. The red blood count and hemoglobin remain normal and only on rare occasions is an immature blood cell seen. The clinical picture is one of chronic fatigue and recurring ulceration of the mouth and throat. Each infection in this case is associated with a severe leukopenia and it is quite definite that the leukopenia precedes the appearance of any ulcerative lesions. As shown in Fig. 284, various nucleic acid

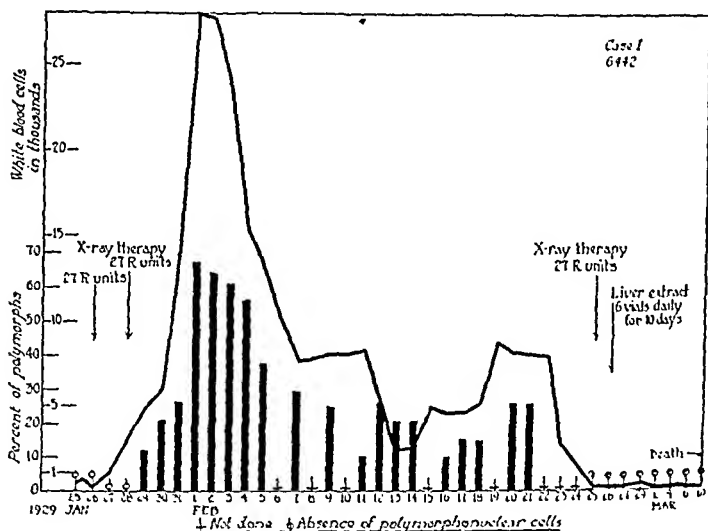


Fig. 284.—Malignant neutropenia, a white woman, aged twenty-seven, showing the rapid course of the disease. x-Ray therapy was followed by a marked leukocytosis which gradually fell off until death.

derivatives, both oral and intramuscular, also liver extract, intramuscularly, were used in this case. During three relapses associated with a severe leukopenia, only supportive measures were instituted. In each of these instances infection was followed by an elevation in the total leukocytic count. It is shown in this case that all forms of specific therapy tried resulted in a myelopoiesis. However, during the course of the nucleotides and liver extract preparations, the elevated count did not persist, but rapidly fell although the same dosage was continued daily.

tory for 'a two months' vacation. During this period the blood was not followed and there were presumably two relapses based on clinical symptoms. On August 21, 1933, she again felt badly and the mouth showed the characteristic serous ulcerations and bleeding gums that had been noted throughout the course of the illness. The blood picture at that time was 98 per cent mature lymphocytes and 2 per cent polymorphonuclear cells. Ten days of nuclein therapy brought forth no improvement in the blood picture. On August 31st she was started on liver extract intramuscularly 3 cc. daily. On the second day after the liver extract had been instituted the count was 3100 leukocytes with 12 per cent polymorphonuclear cells. The count apparently had already started to rise; however, it continued to a total of 4000 leukocytes and 40 per cent polymorphonuclears. This count was not sustained and promptly dropped to 2000 leukocytes and 10 per cent granulocytes on September 12th even though the liver had been given daily to this time. She was admitted to the hospital on September 14th in a stuporous condition and showing typical mouth ulcerations. Only symptomatic treatment was instituted and there were no polymorphonuclear cells seen for seven consecutive days. The count rose spontaneously to a level of 5400 leukocytes and 40 per cent polymorphonuclears, and she was discharged. Was again admitted on October 18, 1933, with 1800 leukocytes and no polymorphonuclear cells. This time she was given pentose nucleotide K-96 10 cc. doses over a period of fifteen days and on the fifth day there was marked improvement in the blood picture. A peak count of 5500 leukocytes and 40 per cent polymorphonuclear cells was attained on the eighth day, but the count started falling immediately and on November 6th it was 3300 with 12 per cent polymorphonuclears. Between each of the 12 recognized relapses the count has averaged 2600 leukocytes and 16 per cent polymorphonuclear cells which approximates this individual's normal level.

This type of neutropenia has been recognized much more frequently in the past few years. It represents the chronic form where the blood count fluctuates between a moderate and

SUMMARY AND CONCLUSIONS

Neutropenia is a descriptive term which in the light of our present knowledge describes the clinical picture that is commonly designated agranulocytic angina. The disease exists in several different forms. The first case presented corresponds with findings and the outcome as originally described by Schultz.¹ The second is an irregularly recurring neutropenia characterized by its chronicity. No etiologic agent has yet been found for this disease complex although several have been suggested, all of which are hypothetical. Madison³ has stressed particularly the importance of the barbituric acid derivatives and drugs containing the benzene ring as the causative etiologic factor. He has shown clearly that a neutropenia which has developed in certain patients who have used these preparations, disappears after the withdrawal of the drug. It is probable that the barbiturates only exert a host reaction in such cases. Neither of the two cases presented gave a history of taking these preparations before their illness. In Case II sodium amytal administered during the course of the disease did not alter the blood picture.

As regards the various therapeutic agents tried, liver extract and blood transfusions in Case I, that of the primary malignant type, had no effect whatsoever. Following x-ray therapy there was an immediate clinical improvement of the patient and a marked leukocytosis with a normal polymorphonuclear ratio, both of which gradually fell until the death of the patient. The explanation offered is that the granulopoietic tissue was drained of all of its former elements and did not have the ability to replenish its supply, as the necropsy showed no active myeloid tissue. Doan² has found in his experiments on pigeons that an increase in the white blood cell count resulting from irradiation of the bones was always accompanied by necrosis of the myeloid tissue.

In Case II of primary chronic neutropenia, the following therapeutic agents were used, sodium nucleinate, nuclein solution, pentnucleotide and liver extract. All preparations were administered intramuscularly except sodium nucleinate which

was given by mouth. It is to be noted in Fig. 285 that all had the ability to raise the white blood cell count and the number of polymorphonuclear cells. After reaching the peak, the level was not maintained, but fell rapidly, although the therapy was continued at the same rate. It was found also that the white blood cells and the polymorphonuclears responded in the same manner to any infection.

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ing 12 per minute about two and one-half hours after the oxygen was started. The oxygen was kept on for forty-eight hours continuously. The patient was kept quiet by morphine, $\frac{1}{6}$ grain every six hours. There is no evidence that oxygen relieved the pain.

The day after the attack the following history was obtained: He had been bothered for two or three years with a sense of constriction in the chest, mostly after meals or on exertion. On this account he had given up handball in 1931, and golf the following year. In the spring of 1932 he had an attack of pain in the chest with dyspnea which came on during sleep. He was in bed at that time for about ten days. There had been more of these attacks at night but they had not been so severe. More recently the pain after meals became worse. Hoarseness after meals, after talking in public, and on fatigue was a more recent complaint. He habitually smoked many cigarets, drank moderately, and took little rest. He knew he had had some elevation in blood pressure for three or four years, yet he got additional life insurance in 1930.

On examination the second day in the hospital comparatively little was found. He was orthopneic, but breathed the enriched air with ease. The lungs were resonant throughout with coarse moist râles everywhere. The apex beat could not be felt. The cardiac dulness came almost to the nipple line. The base was resonant. The heart tones were regular, of fair quality and without murmurs. The abdomen was rounded and soft. The liver edge was palpable just below the costal margin. The rectum was constricted, apparently the end-result of an old operation for hemorrhoids. No sign of focal infection was found. The initial blood pressure taken during the attack was 130/90. Next day it fell to 86/72. It gradually rose so that on the fourth day it was 112/82, but on the fifth day, when the temperature reached its peak of 100.8° F., it again fell to 90/72. After the eighth day it has stayed constant at about 110/80.

The pertinent laboratory findings included a trace of albumin in the urine with an occasional hyaline cast. The white

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OXYGEN IN ACUTE CORONARY OCCLUSION

THE clinic today deals with the use of oxygen in acute coronary occlusion. The three patients will be discussed with the idea of supplying all vital tissues with oxygen and a short explanation for its good offices will be presented.

Case I. Coronary Occlusion with Acute Pulmonary Edema.—At 8.50 P. M. on last November 21st, this man, a robust active sales executive, aged forty-two years, was just ending a talk to a large group of his men. He became tired and hoarse, noted a fulness in his chest and then a difficulty in breathing. He walked to the next higher floor to a couch, but could not lie down and could scarcely breathe sitting upright. His associates held him thus while he gasped for breath and spat up a white frothy sputum. Cyanosis was marked, the veins in his neck were collapsed. The pulse was very rapid, about 160, and weak. Respirations were about 36 a minute and labored. All the accessory muscles of respiration were in use. In the emergency morphine sulphate $\frac{1}{3}$ grain, and atropine sulphate $\frac{1}{30}$ grain, was given. Tourniquets were applied to all four extremities for a few minutes. As the dyspnea began to subside he complained bitterly of a painful constriction in his throat. He was rushed to the hospital. There oxygen was started by nasal catheter, he was kept sitting up, and heat was applied to his body as in the treatment of shock. The cyanosis began to diminish and the tracheal râles and wheezing subsided rapidly. The pulse rate fell so that at 9.30 it was 140, at 10.15, 124, and at 11.30, 116 per minute. It fell to 96 the next morning. The respirations became slow reach-

sugar found in his urine for at least six years. There was difficulty from prostatism in 1932 with periods of retention and nocturnal incontinence. This now causes no trouble. In 1925 he was in bed for about two months with ascites and fever.

He was first examined on November 17th. He weighed 165 pounds, and was 61 inches tall. He was afebrile. The pulse was 104, respirations 18, blood pressure 132/86. The teeth were discolored but the gums appeared in fair condition. Three teeth were crowned. The chest was robust, symmetrical and resonant. There were a few râles at the right base posteriorly. The apex beat was barely palpable in the fifth interspace just outside the nipple line. The heart tones were regular, of good quality, and a systolic murmur was easily heard at the apex. The venous pressure did not appear increased. The abdomen was fat and soft. The liver edge came down to 5 cm. below the costal margin in the nipple line. The brachial, radial and posterior tibial arteries felt soft. The urine had a specific gravity of 1018, was clear, contained a trace of albumin and a few pus cells. The diagnosis at that time was arteriosclerotic heart disease, with angina pectoris, and early congestive heart failure.

On November 28th at about 2.30 in the morning he was awakened with a rather severe pain over his heart. Nitroglycerin brought no relief and in a short time $\frac{1}{6}$ grain morphine was given by mouth. This made him comfortable but did not entirely relieve the dyspnea which came at the same time. He stayed in bed most of the day and ate little. That afternoon his pulse mounted to 132 and at six in the evening he had a temperature of 100.8° F. His blood pressure had come down to 112/86 by that time. The respirations remained about 30 per minute even while sitting up in bed, and were irregular and periodic. A trace of cyanosis was apparent. About 9 o'clock oxygen was started by the nasal catheter and continued for forty-eight hours. Shortly after the oxygen was started he began to breathe easily and regularly at about 22 times per minute. The cyanosis diminished rapidly and by the next day was scarcely apparent. The pulse rate fell in the

count reached 15,500 the day of the greatest fever. A roentgen plate made at 2 meters showed the heart to be of entirely normal size, and both lung fields clear. The blood Wassermann reaction was negative.

He has been a cooperative patient and is still in bed except for sitting up on the edge of the bed thirty minutes each day and getting massage each morning. He is no longer orthopneic, and the only abnormality seems to be a few râles over the right lower lobe posteriorly.

Case II. Coronary Occlusion with Dyspnea and Circulatory Failure but Little Pain.—Mr. C., age sixty-three, an Italian musician, composer, and carpenter, has complained of substernal pain on exertion and after meals for six or eight months. At first the pain came on almost immediately after eating, especially the larger meals. It would last from two to fifteen minutes and would disappear on resting. The pain did not radiate. Not every meal caused the distress which came perhaps three or four times a week during the first several weeks, but after July it was an everyday affair. An x-ray study of the stomach and duodenum was made during the summer but showed no pathology. A story of dyspnea on exertion was brought out only by questioning. It made him stop on steps, or if he hurried, but he considered it of no importance. After October 1st he was not so well. His ankles swelled a trifle and he developed a cough, especially at night. The use of some extra pillows seemed to relieve the cough. The pain also changed, becoming more severe, and a constricting pain appeared in the right wrist along with the pain in the precordium. Nitroglycerin was taken whenever the attacks lasted longer than a few minutes. This drug brought complete relief. He noticed that a glass of wine with his meals made him feel better afterward. The edema of the ankles increased in the latter part of November and he voluntarily stayed indoors.

The past history brought out that he had had diabetes mellitus ten or fifteen years ago which was treated for a time with qualitative restrictions in his diet. There has been no

is bedfast, orthopneic. He has had heart trouble with attacks of spontaneous dyspnea so that he has been entirely helpless for three years. He has had syphilis for thirteen years with very little treatment. His heart is greatly enlarged; you can see the apex out in the anterior axillary line. He has just had his lunch, perhaps he is going into an attack. Yes, the breathing is increasing in depth and rate, you see the flush on his face. He reaches over his heart and is obviously in great pain. He has become slightly cyanotic. You notice he reaches for the oxygen mask, places it in his nose, and then turns the valve himself. You notice the breathing becomes slower, deeper and even, the flush disappears and he seems to relax. He is breathing oxygen with 5 per cent carbon dioxide added. This makes hyperventilation appear. This gas is more effective than pure oxygen in this patient and regularly relieves the difficulty in breathing. The relief of pain is not so constant. If the attack is mild the hyperventilation is followed by relief of the pain. However it is so severe that morphine is needed almost daily. How does that affect you, Henry?

PATIENT: "It lets me get my breath and in a few minutes the pain lets up. I always lose my breath first and then get the pain. The pain goes away last."

In this man oxygen and carbon dioxide is more effective than tourniquets, than nitroglycerin, and is second only to morphine in relieving the attacks of cardiac asthma. The attack you have just seen is one of the milder ones. To describe the remainder of his findings, he has all the manifestations of an aortic regurgitation, a blood pressure reading of 150/0 and the electrocardiogram shows the ST interval well below the isoelectric line.

These three cases have in common a faulty blood supply to the heart and acute seizures of dyspnea, pain and failing circulation. At the time of the acute attacks, as Sir Thomas Lewis has convinced us, there is a true anoxemia of a part or all the heart muscle, whose blood supply is cut down, or in places cut off entirely. The pain comes from muscle working too long without oxygen. In the coronary arteries the blood

first two hours to 118 and he became more composed. Morphine was given hypodermically but he sank into a lethargic semistupor so that drug was discontinued. A soft pericardial friction rub was audible at the apex on the fourth day. By that time the pulse was down to about 100. The temperature was still above 100 but the patient was no longer cyanotic and appeared much improved. Oxygen was continued intermittently for an additional seventy-two hours. On the sixteenth day in bed a pericardial friction rub became quite marked at the apex and persisted for about five days. He had two attacks of precordial distress after being in bed two weeks. The attacks were of short duration, but he received oxygen each time for the duration of the pain. The blood pressure has remained about 116/86 since the fifth day, but reached a low point of 104/76 during the severe illness.

On the fifth day in bed he began to be bothered with hiccoughs. These persisted off and on for about a week and were quite distressing. The only time they came was after eating. Anything over a few ounces would start the singultus. Since he has had no such trouble before or since we felt it indicated an irritation of the diaphragm, probably on the basis of a pericardial inflammation overlying an infarct.

In both of these cases oxygen therapy was begun because of evidence of arterial anoxemia, a central type of cyanosis. Its effect appeared in short order, that is, a lessening of the cyanosis and a drop in the pulse rate with the respirations slowing and becoming more regular. Probably our experience with cyanosis in these cases as a bad prognostic sign had much to do with starting the oxygen just as soon as the coronary nature of the case was apparent. Of course in addition, the men received the usual measures of care to see that they kept absolutely quiet and placed the very minimum demand on the heart.

Case III. Aortic Regurgitation with Paroxysms of Dyspnea and Anginal Pain.—The third case may show us a little excitement. He is twenty-seven, of Irish origin, and

The inadequate oxygen supply in the heart during the stage of pulmonary edema was brought about by the lowered blood pressure, the resistant rigid arteries and an arterial blood not saturated with oxygen. Every factor is out of line. We cannot well raise the blood pressure beyond a low normal figure. We cannot dilate sclerotic coronary arteries effectively, but we can enrich the arterial blood with oxygen so that every part of the heart receiving any blood supply at all will get an abundance of oxygen.

The critical time in the formation of an infarct is the first few minutes or hours that the blood supply is cut off. The cells deprived of oxygen die promptly. In the heart this may be minimized by permitting even what collateral circulation is available, along with the thebesian vessels, to carry blood laden with oxygen under an increased diffusion pressure. If the size of the infarct is reduced even a fraction the effect is worth while.

Coronary occlusion cases without pain are not uncommonly overlooked even with all the attention that has recently been paid this subject. Dyspnea and orthopnea occurring suddenly in older people, with an elevated pulse rate and restlessness are enough to indicate oxygen therapy. It is only recently that acute pulmonary edema has been considered a sign of coronary thrombosis with myocardial infarction.

Summary.—The relief of dyspnea, cyanosis and restlessness in two cases of coronary occlusion is attributed to the use of oxygen. The oxygen is beneficial in supplying all the myocardium to which circulation is maintained with arterial blood bearing oxygen under an increased diffusion pressure. Hence any collateral circulation and the thebesian vessels function more effectively in minimizing the size of the infarct.

flow takes place during diastole when the myocardium relaxes. In the man with the aortic regurgitation the attacks represent a deficient arterial blood supply, that is, inadequate oxygen to all the heart, for his diastolic blood pressure is too low to maintain much of a coronary flow. This is particularly true where the coronary openings have been constricted by a syphilitic aortitis. His attacks begin with dyspnea reflecting a central effect of some disordered respiratory control and continue with precordial pain, possibly brought on by the increased exertion of deep breathing. If the dyspnea is checked by breathing oxygen or oxygen and carbon dioxide mixture, the pain is minimized if it appears at all, but in case the very exhaustive efforts to breathe are continued, his pain will persist for a longer time, until morphine is required to break the circuit. Little moisture is present in his lungs. The slight cyanosis is checked. The entire result is as if the arterial oxygen tension is slightly increased, the dyspnea subsides and the attack is aborted.

In Case I the condition was an acute pulmonary edema brought on by a failure of the left ventricle to empty entirely, while the right ventricle kept pumping blood from the venous reservoirs into the lungs. Such left ventricular failure is due to an acute obstruction in one of the coronary arteries so that a part of the musculature receives little or no blood. From this acute anoxemia an infarct forms. The coronary circulation to the rest of the heart is none too good, for undoubtedly the remaining arteries are sclerosed and rigid. Moreover, the diastolic blood pressure was lowered from the shock of the attack. Cyanosis had appeared because of stasis in the periphery and also because of the edema in the lung. Oxygen in the alveoli had a layer of edema fluid, a transudate, to retard its passage into the capillaries. An increase of partial pressure of oxygen in the alveoli overcomes the "dampening" effect of the edema. Thus blood left the lungs saturated (99 per cent) with oxygen and carrying this oxygen at a higher tension, a greater diffusion pressure than air could give. In this patient it seems that the oxygen did just that, for the cyanosis diminished rapidly, but it also benefited the heart,

panied by nausea and vomiting. The patient did not remember having had chills or fever. The appetite had remained good and there had been no weight loss. During the past five months she was conscious of a sensation of gas passing from the urethra during urination.

The positive physical findings were chiefly those revealed by rectal and vaginal examination. A hard, irregular, somewhat fixed mass was found to fill the left half of the pelvis. On proctoscopic examination, a constriction of the bowel was encountered at about 20 cm., at which point there was a redundancy of the mucosa, but no ulceration was seen and the instrument could not be passed further. At cystoscopy an area of bullous edema was seen above the trigone about 3 cm. in diameter from which pus was exuding.

The laboratory findings were as follows: The blood Wassermann and Kahn tests were negative. Blood count was normal. The urine contained large numbers of pus cells. The stools were negative for occult blood by the benzidine test. Roentgenological examination of the colon with the barium enema demonstrated a gross obstruction at the junction of the pelvic and descending colon, through which only a tiny stream of barium could be made to pass. In the roentgenogram the stenosed section was visible and a thin barium tract was also seen extending from the site of the obstruction downward into the region of the bladder. No diverticula were noted.

At operation the lower portion of the sigmoid was found indurated, constricted, and adherent to the fundus of the urinary bladder. It was dissected off, and in so doing a fistulous tract was discovered. The opening in the bladder was repaired and that portion of the sigmoid containing the mass brought outside the abdominal wall by the Mikulicz procedure. No diverticula were found in the rest of the colon. On the fourth postoperative day, the exteriorized involved portion of the sigmoid was removed by cautery. Further convalescence was uneventful. Microscopical examination of the lesion demonstrated no evidence of malignancy. In the gross specimen there was only one diverticulum.

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THE DIFFERENTIAL DIAGNOSIS BETWEEN DIVERTICULITIS AND CARCINOMA OF THE RECTOSIGMOID

THE two cases to be presented here have been chosen to illustrate certain difficulties in the diagnosis of carcinoma of the rectosigmoid when associated with diverticulosis and chronic diverticulitis with tumefaction.

Case I.—Mrs. F. W., aged sixty-four, entered this hospital on October 10, 1933. Except for a right mastectomy for recurring abscesses ten years ago and a hysterectomy for a uterine tumor fifteen years ago the past history was negative. Her story at the time of admission to the hospital was that during the past three years she had had recurring attacks of lower abdominal pain. These at first came on every few months but gradually increased in frequency and severity. The last attack occurred ten days before entrance. For two days preceding each attack there was a feeling of lassitude and a vague abdominal distress followed by a sudden severe continuous pain in the left lower abdomen radiating to the lower back and accompanied by intermittent cramping. These symptoms lasted for about twenty-four hours and were relieved only after administration of morphine. During this time it was difficult for the patient to have a bowel movement and there was always an intense urgency and frequency of urination. The urine was usually dark and scanty and, in some instances, contained gross blood. On one occasion two years ago she passed gross blood from the rectum. This attack was also accom-

normal. The gastric content after an Ewald meal was found to contain a free acidity of 30 and a total acid of 60 clinical units. The stools were mixed with mucus and considerable gross blood.

On roentgenological examination of the colon with the barium enema, a definite delay was noted in the filling of the rectosigmoid and on further examination a definite deformity could be seen involving 8 to 10 cm. of the colon. Multiple diverticula were observed in the lower portion of the descending colon and in the sigmoid.

It is important to note that biopsy specimens taken from the lesion at the time of the proctoscopical examination showed at first evidence of an inflammatory reaction only but after further sectioning definite carcinoma was demonstrated.

On the fourth day after admission, the patient developed an acute thrombophlebitis of the left saphenous vein which subsided in the course of a week. Because of this complication, operation was postponed for about two weeks. During this interval a diet low in residue but high in calories was given and ferric ammonium citrate, 6 Gm. daily, because of the anemia. A blood transfusion was deemed inadvisable in the face of the thrombophlebitis. The rectal bleeding subsided considerably, and with the improvement in the patient's general condition it was decided to attempt surgery. At operation the rectosigmoid tumor was fixed in the culdesac and the hollow of the sacrum. There were many small diverticula along the course of the transverse and descending colon. Extending up from the tumor were numerous areas in the sigmoid and descending colon in which the diverticula were inflamed. The mesentery of the sigmoid contained numerous large masses which were carcinomatous. A cecostomy was done as the tumor was thought to be inoperable. The right upper quadrant mass felt on physical examination was found to be a distended gallbladder containing a cystic duct stone. The patient had a rather stormy postoperative period, but gradually recovered sufficiently to leave the hospital.

Case II.—Mrs. B. B., a fifty-six-year-old housewife, entered the hospital on November 2, 1933. Until eight months previous to her admission she enjoyed good health. In March of this year she began noticing an increasing loss of appetite and with it a gradual loss of 45 pounds in weight. She always experienced some difficulty in keeping her bowels regular but, with the onset of the above symptoms, this became more marked and was accompanied by considerable abdominal distention. The stools became small and contained gross blood. Desire to defecate grew more frequent averaging five to ten times a day, but for the greater part the movements consisted chiefly of gas and blood. She consulted her family physician in June and, after roentgenological examination of the colon, was told that the bowel contained numerous outpocketings and showed signs of inflammation. She was placed on a soft diet but the distress continued to increase so that during the last two months before admission there was severe intermittent cramping over the entire abdomen, pain in the lower back, and marked tenderness over the left lower quadrant. Gradually the amount of blood passed had increased so that during the last two weeks she passed "at least a cupful" with each movement.

On entrance the patient appeared ill. There was a marked pallor of the skin. A small globular respiratory movable mass was palpated in the right upper quadrant of the abdomen. Marked tenderness was elicited over the descending colon and sigmoid. There was no distention or abnormal peristalsis. A hard irregular mass was palpated on rectal examination. Through the proctoscope an ulcerated cauliflower-like growth almost occluding the bowel lumen was seen at 12 cm. above the anal ring. The bowel mucosa otherwise appeared normal.

The laboratory findings were as follows: The Wassermann and Kahn tests were negative. The leukocytes numbered 10,600 per cubic millimeter. The erythrocytes numbered 2,960,000 per cubic millimeter of blood with moderate hypochromasia. The hemoglobin was 7.4 Gm. (Newcomer) and 44 per cent by the new Dare method. The urinalysis was

hospital, whereas in carcinoma the symptoms are more recent in onset, eight months in Case II. The average, according to various writers, is from eleven to twelve months. Acute attacks of pain are observed more frequently with diverticulitis. Constipation of varying degrees is common in both conditions. Urinary disturbances, such as frequency and urgency, are more often observed in diverticulitis.

Bleeding from the rectum is probably one of the earliest and most significant signs of carcinoma of the rectum and sigmoid. However, there are instances in which the lesion has attained considerable size before this symptom occurs. When bleeding does occur it is constantly present to varying degrees, and may at times reach a rather alarming state as shown in the history of Case II. Rectal bleeding is seldom a symptom in diverticulitis. It occasionally occurs, however, but not to the degree manifested in carcinoma. In Case I, rectal bleeding occurred on only one occasion and was probably due to the perforation. Even though the tumefaction had reached considerable size and the amount of obstruction was marked, there was no gross or occult blood present in the stools of this patient at the time of her entrance to the hospital.

Loss of weight and strength are also significant factors in differentiating between benign and malignant lesions as is well shown by the fact that in the first patient there had been no weight loss even though the symptoms had been of three years' duration whereas, in contrast, the second patient had lost 45 pounds and had become markedly weakened during only eight months of symptoms. Occasionally one does encounter a patient with a rather large neoplasm of the rectum or sigmoid without apparent loss of weight or strength.

An impression quite commonly held is that a change in the caliber and shape of the stool is indicative of malignancy in the rectum or lower sigmoid. This is not always true for a common complaint of patients suffering from chronic constipation is that of small or ribbon-like stools. On the other hand, in neither of these two cases could a definite history of this

DISCUSSION

Since Cruveilhier's description of diverticulosis of the large bowel a great deal has been written regarding this interesting condition. It is generally conceded that diverticula as such do not produce disturbances of the intestinal tract. It is not until inflammation occurs that the individual experiences difficulty. Diverticula may be single or multiple, and occur in all age groups although they are most common in older individuals. The cause and method of formation of diverticula is still disputed. It is the general opinion, however, that these small outpocketings along the course of the large bowel are acquired rather than congenital and that they occur along the mesenteric attachment where the blood vessels enter the bowel wall. But regardless of the manner of origin, the first symptoms noted are those associated with the inflammatory process, the diverticulitis, which probably results from the retention of intestinal content in one or more of the pouches.

The symptoms of diverticulitis of the sigmoid vary from mild attacks of pain, usually in the left lower abdomen, to those phenomena arising from the graver complications of the disease such as perforation, stricture, and fistula formation. It will be remembered in the presentation of the history of the first patient that there were recurring attacks of left lower abdominal pain which became more severe with each succeeding attack. As the inflammatory process continues and tumefaction develops, more and more obstruction of the bowel occurs with its resulting symptoms. Thus in a patient giving a history suggestive of bowel obstruction, the differential diagnosis of chronic diverticulitis, carcinoma, and other types of obstruction immediately arises. When a tumor mass is present it may not be possible to differentiate by palpation the old fibrosed inflammatory mass of diverticulitis and the hard nodular growths of carcinoma.

The history when carefully taken may be of considerable help. As a rule the story dates back over a longer period in diverticulitis, as for instance in Case I in whom the onset of symptoms occurred three years previous to her entrance to the

other condition than carcinoma. An inflammatory or infectious process involves the mucosa of large areas or the entire bowel. A malignant lesion is nearly always single, it is often associated with polyps. The mucosa about it appears normal. In the second case, the proctoscopical appearance of the lesion was so definitely that of a malignancy that the pathologist's



Fig. 286.—Roentgenological appearance of colon of Case I, following barium enema and air inflation. 1, The area of obstruction; 2, the arrow pointing to fistulous tract.

first report of an inflammatory process was doubted and further study of the biopsy specimen requested. The mistake of taking a biopsy too near the outer confines of a lesion is sometimes made, thus causing errors in the pathologic diagnosis. One should obtain a specimen from well into the growth.

Mention should be made of other laboratory procedures

nature be obtained. This may have possibly been due to the use of some type of catharsis to keep the stools soft.

The presence of a vesicocolic fistula as indicated by the history of passing air through the urethra in the first case is not an infrequent complication in diverticulitis. Perforation occurs also in the presence of carcinoma but not nearly with the frequency found in cases of diverticulitis. In a Mayo Clinic series, perforation of the bowel was encountered in 10 per cent of cases of malignancy and in about 50 per cent of the cases of diverticulitis. Of the latter group, vesicocolic fistula was found in 14 per cent of the cases operated on.

Examination of the abdomen may not give much information. If the tumor is well out of the pelvis it may be palpable. In emaciated or rather slender individuals, increased visible peristalsis would suggest obstruction of the bowel. In neither of these cases was there an abdominally palpable mass or indication of increased bowel activity. The most significant positive physical finding in each of the two patients was that obtained on digital rectal and vaginal examinations. In each the mass was large, hard, fixed, and irregular. In the first case it was difficult from these examinations alone to definitely make out whether the bowel was the primary organ involved. The uterus had been removed twenty years previously, but a primary tumor of the adnexa had to be considered. The result of a rectal examination in the second case was not so difficult to interpret since the mass was more easily palpable and considerable bloody material adhered to the glove of the examining finger.

A proctoscopical examination, where possible, should always be done when rectal or sigmoid pathology is suspected or found by palpation. It not only enables one to visualize the process but it also affords an opportunity to obtain a biopsy. Unfortunately, as sometimes happens when the bowel is more or less fixed by the surrounding mass, proctoscopy in the first patient did not give conclusive evidence as to the nature of the lesion. When a proliferating mass, such as was found in the second case, is seen it can hardly be confused with any

diagnosis, the roentgenological examination affords an extremely valuable link in the chain of evidence but it must not be considered infallible.

The treatment employed in these two cases for obvious reasons was surgery. This was necessary in the first case because of the amount of bowel obstruction in addition to the



Fig. 287.—Roentgenogram of the colon of Case II, following barium enema and air inflation. Arrow points to upper and lower limits of the lesion. Note the numerous diverticula.

complication of vesicocolic fistula. Operative procedures in diverticulitis are accompanied by a rather high mortality, ranging among various surgeons from between 10 to 12 per cent. Because of the possibility of spreading the infection to other parts of the abdominal cavity, surgeons are not inclined to operate in cases of uncomplicated diverticulitis. In the second

of importance. The blood count may be very significant. Anemia associated with diverticulitis if present at all is only slight and certainly not to the degree frequently found in patients with a malignant lesion, as illustrated by the marked secondary anemia observed in Case II.

Roentgenologists feel that to differentiate between diverticulosis and carcinoma is relatively easy. This is true as long as the tumefaction has not assumed such proportions as to occlude the bowel lumen completely or nearly so. Generally in the inflammatory process there are signs of irritability and spasm while the mucosal folds appear broad and the haustrations are irregular. In addition the barium-filled sacculations typical of diverticulosis are usually found. When obstruction occurs the outline of the involved area is smoother in comparison to the sharply irregular filling defect of carcinoma. A longer segment of bowel is usually involved in diverticulitis than in carcinoma. Comparing the roentgenological manifestations of the lesions found in the two cases presented, the incorrect diagnosis of malignancy would probably be made in the first patient and that of diverticulitis in the second. In the former, the obstruction was practically complete and the segment of bowel involved quite short while above the occlusion no diverticula could be demonstrated (Fig. 286). The bowel of the second patient, on the other hand, was studded with diverticula, especially in the region of the obstruction. This lesion involved a somewhat longer segment of bowel and its outlines were irregular (Fig. 287). Thus the roentgenological findings were the reverse of those one would expect from the history and physical findings. Carman made the statement that "in the instance of carcinoma supervening upon diverticulitis, if rounded extraluminal shadows are present, the lesion could not be distinguished from a benign diverticulitis, while if these shadows were not present the case would probably be regarded simply as one of carcinoma." It can be seen, therefore, that in these two cases at least, to have depended entirely on the roentgenologists to make the diagnosis for us would have led to some confusion. In formulating a clinical

case, the symptoms, physical and pathological findings all pointed to the presence of a malignant lesion producing obstruction of the rectosigmoid. It was necessary, therefore, to attempt either resection of the involved portion or, at least, to relieve the obstruction. Both patients survived their operations. The first should experience no further difficulties, while the second patient continues to fail.

From the foregoing discussion it is evident that no single symptom, physical sign or laboratory finding is pathognomonic of either diverticulitis or carcinoma, except perhaps a biopsy properly performed and examined by an experienced pathologist. On the other hand, if one gathers together all of the data afforded by the various diagnostic measures and carefully correlates them with the history and physical findings, it is usually not difficult to arrive at the correct diagnosis. Fortunately, the rather complicated situations presented in the two cases described above do not arise frequently. It is important to bear in mind that any patient complaining of symptoms associated with a change in the normal bowel function deserves a careful and painstaking examination to exclude an organic lesion.

cult to determine whether the relationship of the infection to the purpuric tendency is primary, secondary, or coincidental.

A consideration of the history of our case will illustrate this association.

Case.—This patient, a white male, age thirty-eight, is a candy salesman. He came to the dispensary on January 21, 1933, complaining of hematuria of seven days' duration, bleeding from the gums for ten days, and loss of strength, anorexia, and nausea and vomiting since an attack of influenza around January 1, 1933.

The patient states that he had influenza around the first of the year and was in bed for two weeks. Following this, the patient has been very weak and one week ago (January 13th) he noticed blood in his urine and began to bleed from his gums. The urine cleared up (no visible blood) in one week, but the bleeding from the gums has continued.

In his past he had an attack of scarlet fever at the age of three with "dropsy" and he dates most of his troubles to that time. His parents have no knowledge of his bleeding prior to that time, and to the patient's knowledge there is absolutely no history of "bleeders" on either side of the family.

About one year following the scarlet fever, the patient had his tonsils removed and almost "bled to death." This is the first knowledge that the patient had of his trouble. Since that time the patient had been troubled with "bleeding from the nose" up until two years ago. During the past two years, up to the time of the present complaint, he has had no hemorrhages. He has bled from the kidney on two separate occasions; the first time two years ago following an injection of diphtheria antitoxin, and the second time last week.

The mother of the patient, when interviewed, stated that the history of "bleeding" dates back to about the age of three. Following scarlet fever, the patient received a bruise on the abdomen which became "black and blue" and persisted for several weeks. At the age of nine he had a tooth extracted and bled for six months. Any little bruise would cause a black and

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THE INFLUENCE OF FUSOSPIRILLAR INFECTION ON THROMBOCYTOPENIC PURPURA

THE term purpura, as applied to conditions characterized by bleeding from mucous membranes and into the skin, is descriptive in a majority of cases of a symptomatic hemorrhagic tendency, secondary to some underlying morbid state. Thus, in certain intoxications, in cachectic states, in infectious diseases, in senility, as a result of certain nervous disorders, and in obstructions to circulation, the bleeding tendency is obviously a result of the underlying pathologic process.

We assume that this secondary or symptomatic type is an expression of capillary injury or is a result of the action of infection or intoxication on the bone marrow, spleen, and reticulo-endothelial system.¹

However, a number of these hemorrhagic cases characterized by definite blood changes cannot be ascribed to any underlying diseased condition and must be considered as a primary or essential disease by itself.

Essential thrombocytopenic purpura is a disease of the reticulo-endothelial system with probable destruction of platelets by the spleen and marked interference with normal platelet formation in the bone marrow. As our knowledge of this group increases, we should find a diminishing number whose etiology cannot be explained.

Some of these cases are often associated with morbid infectious lesions in the mouth and throat of such a severe character that the clinical picture is confused and it may be diffi-

low the free margin of the gum. This was mainly of the dark, hard type known as serumal calculus.

The pharynx was congested. There was a swollen, necrotic area over the region of the right tonsil stump, which interfered with swallowing. The anterior chains of cervical lymph glands were enlarged and tender.

The chest examination showed no axillary enlargement. The heart was within normal limits, tones regular, of good quality, and no murmurs. The lungs failed to yield any abnormal findings. Abdominal examination showed no palpable masses, no tenderness, no rigidity. The liver and spleen were not palpable.

There were subcutaneous hemorrhagic areas on the right leg. Reflexes were all normal.

The temperature was 100.4° F., pulse 112, respirations 20, blood pressure 130/70.

His blood picture was as follows: hemoglobin 10 Gm., red blood cells 4,800,000, white blood cells 14,700. Differential count:

Polymorphonuclear neutrophils.....	76
Mononuclears.....	2
Lymphocytes.....	21
Myelocytes.....	1

Coagulation time twenty-five minutes. Bleeding time two hours. Platelets 44,000. One nucleated red blood cell. The clot did not retract after several hours. The platelets showed a variation in size; some were almost as large as a red blood cell.

Thus there is a picture of secondary anemia, some evidence of regeneration, a fairly normal differential ratio, but a marked increase in bleeding time, prolonged coagulation time, a low platelet count and a clot which does not retract.

Urine examination revealed 4+ chemical blood and many blood and pus cells and blood and pus casts. Stool examination showed gross blood.

The tourniquet test produced ecchymoses showing decreased capillary resistance. Blood calcium determination gave a normal value of 10.09 mg. per 100 cc. of serum.

blue mark. He has also bled from the gums on previous occasions.

General and Negative.—His appetite has been poor since January 1st, whereas it previously had been very good. He has been nauseated and has vomited dark material (swallowed blood from mouth?) every morning on awakening since January 1st. Tarry stools, but with no red blood, have been present since January 1st. He has lost 16 pounds since that date. Nocturia has been present three and four times since January 1st, and hematuria for one week starting January 13th; also once previously, two years ago, after the injection of diphtheria antitoxin. Epistaxis had been present prior to two years ago as stated before. He had a previous attack of influenza in 1917, gonorrhea at seventeen years of age. He was diagnosed as hemophilia at the age of eleven.

Physical Examination.—On examination the patient appeared to be a well-developed and fairly well-nourished individual with continuous bleeding from the mouth but did not appear acutely ill or shocked.

The brain and scalp showed nothing abnormal. The eyes reacted normally and the pupils were equal and regular and muscle functions were good. The ears and nose showed nothing out of the ordinary.

The mouth contained an abundance of blood in liquid form and in stringy clots adhering to the gums and teeth. There was a constant accumulation and spitting of blood and saliva in considerable quantity. The gums themselves were firm and pink except for a narrow margin between the teeth and around the gingival borders where they presented a swollen, congested appearance with some ulceration and necrotic membrane formation. The teeth were firm and not tender to pressure, but the ulcerated gingival borders of the gums were painful. The appearance was that of a moderate Vincent's stomatitis or "trench mouth." The greatest amount of bleeding did not come from these lesions but seemed to be a generalized oozing with no particular point of hemorrhage. There was considerable calculus deposited around the necks of the teeth just be-

A second large necrotic patch was noted on the other side in the region of the left tonsillar fossae on March 3rd with considerable swelling. This improved in several days' time when painted with a neoarsphenamine and glycerin solution.

A blood count taken at this time showed the following: Hemoglobin 7 Gm., red blood cells 3,080,000, white blood cells 15,000. Differential count:

Polymorphonuclear neutrophils.....	70
Mononuclears.....	6
Lymphocytes.....	22
Eosinophils.....	2
Reticulocytes.....	3.4%

Platelets 45,000. Bleeding time twenty-five minutes.

He was transfused for the fourth time on March 8th. This was followed by a smart reaction, the temperature going to 101° F., but no chill occurred. A small retinal hemorrhage in the right eye was observed on March 14th. A slight increase in the platelet count to 75,000 was noted on March 16th, probably as a result of liver therapy.

About a week later, the bleeding from the gums was less and the patient felt stronger. He seemed to improve in strength although his gums still bled, and he was allowed to leave the hospital on March 31st with a platelet count of 40,000 and a bleeding time of twenty-five minutes.

After leaving the hospital, our patient remained at home in fair condition but continued to have persistent bleeding of considerable amount from the gums. Liver therapy was continued. At intervals, blood examinations showed improvement and then again remission. April 29th the platelet count was 30,000 and bleeding time six minutes. July 20th the count was 40,000 and the bleeding time eighteen minutes.

The patient was then sent to a dentist and the deposits of tartar were carefully and thoroughly removed and the teeth cleaned. Local medication with peroxide mouth wash and frequent applications of mercurochrome were used. This required seven sittings over a period of eight weeks from July 21st to September 16th, because only a few teeth could be

Smears from the throat lesion showed an abundance of fusiform bacilli and spirillae. The patient was seen by the laryngology department and their opinion was that the throat lesion represented a gangrenous type of infection resulting from the blood dyscrasia.

An opinion from the dermatology department described the pharyngeal lesion as a "membranogangrenous invasion of the right tonsil and uvula and membranous débris on gums," possibly a Vincent's infection superimposed on the purpura.

The patient was given a peroxide mouth wash and 20 cc. of whole blood was given intramuscularly on January 23rd and again on January 24th, 25th, and 29th.

On January 30th it was noticed that the gangrenous area on the right tonsil was larger and the patient complained of a great deal of pain in the throat. On February 1st he appeared weak and exsanguinated, and the gums continued bleeding. The throat lesion remained about the same. Sodium perborate powder was applied locally. A transfusion of 650 cc. of blood was performed on February 2nd following which the patient felt better but still continued bleeding.

Blood and saliva were drooling constantly. He had considerable difficulty and pain on swallowing. In the morning his pillow was covered with blood and he would vomit quantities of bloody vomitus. A solution of neoarsphenamine was used locally instead of sodium perborate. He was again transfused (300 cc.) on February 4th.

Many purpuric spots were observed on the arms, back, and abdomen, and he was unable to retain any food. On February 10th, he developed a hemorrhage into the left half of the tongue. He was still bleeding from the gums and showed purpuric spots over the body and mucous membranes on February 14th, but the tonsillar lesion was markedly improved.

A third transfusion of 200 cc. was given on February 21st followed by a moderate reaction. Liver extract ($\frac{1}{2}$ ounce b. i. d.) was started on March 10th in an effort to stimulate bone marrow activity with the hope of increasing the number of platelets.

serum is squeezed out. In hemophilia, there is a marked tendency to bleed into the joints with permanent joint damage—this did not occur in our patient. The fibrin formation time in hemophilia is prolonged; in this case it was visible in abundance in six to eight minutes. Thus, on close analysis we can definitely rule out hemophilia as a consideration.

Scurvy may be thought of on account of the marked and persistent oral bleeding, but questioning revealed that the patient's diet had been entirely adequate for antiscorbutic vitamin. Our experience with scurvy in adults has been that it occurs in individuals who have been on an inadequate diet for many months before symptoms are manifest. Usually, we have seen it in elderly men, who are bachelors and getting their own meals, and who subsist for a prolonged time on a "bread and coffee" or doughnuts and coffee diet. Occasionally, it has been seen in a peptic ulcer patient who has too faithfully persisted in an exclusive Sippy diet for many weeks or months.

But the appearance of the gums in our patient is not typical of scurvy. Except for the areas around the gum margins and in between the teeth, the gums are not particularly swollen nor soft nor discolored. The teeth are not especially tender nor loose. In scurvy there is a diffuse and marked swelling, the texture is soft and distinctly spongy, and the color is a typical purplish red and "plushlike"² in appearance. There is a marked loosening and soreness of the teeth. Our case shows no scurvy sclerosis—the induration following massive and deep hemorrhage into the muscle groups. The bleeding here is a subcutaneous ecchymosis without induration. In scurvy the platelet count is normal, and this case shows the marked diminution of blood platelets.

Leukemia of the acute type must be thought of, as it frequently starts with an ulcerative sore throat and bleeding. But in leukemia, the lymph nodes are usually enlarged, the leukocyte count is as a rule much higher, and a greater proportion of immature white cells is present. The reduction in platelets is not so marked; the spleen is usually enlarged.

Differentiation from aplastic anemia is to be considered.

treated at a time as instrumentation provoked severe bleeding. There was an immediate and progressive improvement in the gum condition. The swelling and ulceration subsided and the bleeding diminished. The cervical adenopathy decreased. There had been no recurrence of the pharyngeal infection. By the time the dental treatments were finished, bleeding had ceased completely and on October 5, 1933, the blood count showed hemoglobin of 74 per cent and platelets 120,000. The patient had gained weight, felt strong, and active, and worked daily at his old occupation.

To summarize the course of his illness, we may say that he was admitted to the hospital in an obviously precarious condition with marked bleeding from the mouth and kidneys and into the skin; and with a severe fusospirillar infection of the throat and gums. He presented the blood findings of a thrombocytopenic purpura. Upon a three-month régime of rest, local applications of peroxide, perborate, and neoarsphenamine, liver therapy, intramuscular injections of whole blood, and four transfusions, he improved to the extent of feeling stronger and being free of all purpuric manifestations except a few small subcutaneous ecchymoses and persistent bleeding from the gums. His platelet count, however, remained low (40,000), and the bleeding time prolonged to twenty-five minutes.

After returning home he continued to bleed persistently from the gums until thorough scaling and cleaning of the teeth with local treatment of the fusospirochetal gingivitis resulted in relief. General improvement of weight and strength, and specific improvement of the blood picture followed.

With this history and such findings the diagnosis seems clear, but it may be well to differentiate this case from other ailments of a similar character.

One might well consider hemophilia as a possible diagnosis with this history of recurring hemorrhages from early childhood, but there is no hereditary factor at all. The coagulation time was not excessive, and the bleeding time was considerably prolonged. The clot was nonretractile, whereas in hemophilia when coagulation finally occurs, the clot does retract and the

likely is a result of depressed platelet production due to a damaged thrombocytopoietic system.⁴

We may conceive that for normal arrest of bleeding, the capillary endothelium must be in good condition and the blood clot must occur with adequate rapidity and must retract in an adequate manner.

Thus a defect in the continuity of the capillary wall occurring from any cause will be sealed if there are no gaping interstices in the endothelium and if the clot plugs the defect in an effective manner. It is possible that the mural margination of a normal number of platelets helps to prevent escape of blood through the endothelial interstices. If the endothelium is injured, or if mural margination is deficient due to decreased number of platelets, escape of blood may occur (decreased capillary resistance as shown by the tourniquet test). If the clot forms too slowly, as in hemophilia probably due to decreased fragility of the thrombocytes, there is no plug formed to seal a break in the capillary continuity. If the clot does not attach firmly or does not retract normally as in primary purpura, the aperture in the capillary wall is not drawn together and is allowed to gape with consequent escape of blood. In our case the latter situation probably prevails.

We may consider that cases like ours have a condition that is more or less constantly present. It is not unlikely that there is a state of chronic thrombocytopenia. If no unusual infection or trauma occur, he may go along for years in an uneventful routine. But if some severe infection or injury or intoxication should occur, and upset takes place which is manifested by active symptoms of bleeding.

Certain noxae, as Piney⁵ states, will injure the thrombocytopoietic system, which is the most delicate of the myelopoietic ones,⁶ producing "essential thrombopenia." More intense noxae may attack the reticulo-endothelium inducing generalized myeloid aplasia. Destructive stimuli of still greater intensity will injure other endothelium as well, resulting in the picture of "purpura fulminans" in which capillary injury and thrombocytopenia are both present. Such a state may be

We may find a tendency to hemorrhages and a low platelet count in aplastic anemia, but there is also a marked oligocythemia and no evidence of regeneration of cells. The leukocyte count is very low, usually below 2000, and there is an absolute decrease in polymorphonuclear cells and other granular forms, while the lymphocytes are relatively increased. This disease runs a rapid course and is practically always fatal. Our case shows opposite blood findings of a secondary anemia with reticulocytes and nucleated red cells indicative of regeneration, and a high white cell count with a large proportion of granulocytes.

We can conclude that this case fits in best with the picture of primary purpura hemorrhagica of the thrombocytopenic type, and the history and findings are quite typical. There is the history of frequent ecchymosis following slight bruising and of frequent bleeding from the mucosa of the nose and mouth and of several attacks of hematuria. There is the rapid development of anemia, and a leukocytosis. A consistently low platelet count is found. The bleeding time is prolonged with some increase of coagulation time. The blood clot does not retract. The application of the tourniquet produces hemorrhages into the skin.

The question arises as to what is the immediate cause of the hemorrhagic extravasations. Probably different factors or combinations of factors operate in different cases. There are probably alterations in the capillaries which allow the escape of blood into the tissues. A degeneration of capillary endothelium and separation of the cementing substances binding the vascular endothelial cells is probably present in the symptomatic types of purpura as in avitaminosis.¹ Infection accentuates the vascular injury.

The changes in the blood itself are an important factor. The diminution in the number of platelets is undoubtedly responsible to a great extent for the hemorrhages. The cause of the low platelet count may be due to increased platelet destruction by the spleen as claimed by Kaznelson³ but more

In our patient we may logically assume a similar association. Starting in a man with a definite history of a purpuric diathesis, weakened by influenza, in whose mouth are the favorable factors for bacterial growth of poor hygiene and irritation from calculus and food débris, there readily occurs an active invasion of the gum tissues by fusospirillar organisms. This infection by direct extension involves the right tonsillar fossa. The resulting toxic absorption depresses bone marrow function, especially platelet formation, and a thrombocytopenic state with purpuric manifestations is produced.

A protracted course with involvement of the left side of the pharynx results. There is almost constant bleeding from the gums for months with hematuria, ecchymosis in the skin and mucous membranes, and retinal bleeding.

Treatment with rest, diet, injections of whole blood, repeated transfusions, and local medication gives only fair results. Liver feedings help, but complete recovery does not occur until the primary infection in the oral cavity is eradicated.

The student should appreciate that such infections, especially of the fusospirillar type, are likely to assume a virulent character in individuals with blood dyscrasias, and lead to dangerous hematopoietic depression and imbalance. The need of complete and frequent blood study to enable early recognition is obvious.

It has been well said¹⁰ that "prophylaxis rests in the hands of the dentists in the maintenance of good oral hygiene, as well as in the hands of the laryngologist who should be on the lookout for tonsils chronically infected with these organisms."

To this statement we may add that prophylaxis also rests in the hands of the internist who sees cases with history or evidence of blood dyscrasia. It is his duty to warn them of the dangers of infections, especially those due to poor dental and throat hygiene, which may precipitate active manifestations of acute hematopoietic decompensation.

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likened to the diabetic who has a fair sugar metabolism under normal conditions, but is thrown out of balance by any severe strain or infection, with resulting glycosuria, ketosis, or coma.

An analogous condition has been observed in hemophilia. Some hemophiliacs have little or no bleeding until some intercurrent infection causes a sudden increase in coagulation time⁷ and induces a bleeding phase.

In neutropenia, Doan⁸ has shown that there may exist a low myelocytic reserve, that such patients are in constant potential danger of marrow insufficiency and decompensation by the sudden strain resulting from bacterial invasion, and that a relatively minor infection may precipitate a state of lowered resistance and thus represents a primary rather than a secondary factor in the production of neutropenia.

There is evidence to show that toxic injury from drug therapy may depress the hematopoietic mechanism. Thus, arsenical medication (*i. e.*, intravenous injections) may bring on a thrombocytopenic purpura. McCarthy and Wilson⁹ cited 12 cases of this purpuric character and other cases which resulted in granulocytopenia and in aplastic anemia. Several of these cases were associated with angina.

This association with mouth and pharyngeal infection is not uncommon. Usually the infection is of the Vincent's type. The Vincent's organisms—fusiform bacilli and the spirilli—may be normal inhabitants of the oral mucosa and do not become pathogenic invaders unless the resistance of the tissues is lowered by systemic debility, poor hygiene, mechanical irritation from accumulation of calculus and from poor fitting dental restorations and excessive use of tobacco.

In every case of fusospirochetal angina, an attempt should be made to find the systemic or local causes making for increased virulence of the organisms in the opinion of Goldman and Kully.¹⁰ They believe that especially in primary blood dyscrasias in which there is a marked weakening of body defenses does this angina assume serious aspects, and they cite agranulocytic angina, aleukemic leukemia, and infectious mononucleosis as frequently illustrating this relationship.

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1926, she had noticed a bulging in the right upper quadrant of the abdomen, confirmed by the family who could see and feel it. An osteopath diagnosed enlargement of the liver and "pushed it back into place." About the same time (1926) the patient began to suffer from arthritis of the right hand which improved somewhat after the extraction of some teeth in 1927. Since 1928 the patient had been subject to attacks (of pain?) with nausea and somnolence, occurring every two months. She had taken 20 to 30 grains (1.3 to 2.0 Gm.) of aspirin daily for arthritis, and since September, 1930, had used "atophan" in large doses. Neither drug, however, had been taken recently so far as was known.

January 14, 1931, the patient experienced a sharp pain in her right side. On March 4th, her husband noticed that she was jaundiced. From that time until admission she was very drowsy. On March 5th, dark urine and putty-colored stools appeared, and a doctor found the liver one hand's breadth below the costal margin. The jaundice deepened, the drowsiness increased, the patient became nauseated, and on March 10th, 11th and 12th vomited. March 14th she became irrational and sank into coma.

Physical examination revealed a temperature of 98.2° F., pulse of 100 and respirations of 10 to 12. Coma was profound and a deep golden-brown jaundice was present. The heart and lungs were normal. Blood pressure was 124/90. The liver and spleen were not palpated. Liver dulness extended from the fifth to the seventh interspaces anteriorly. There were no petechiae.

Laboratory data showed an erythrocyte count of 4,500,000, a leukocyte count of 10,000 to 18,000 and hemoglobin of 82 per cent. The Wassermann and Kahn tests were negative. The urine contained a trace of albumin and was positive for bile, but urobilinogen was absent.

March 15th, the blood sugar* was 80 mg. per 100 cc. March 16th, the liver dulness disappeared entirely and was

* Blood sugar analyses as performed in this laboratory (new Folin method) yield values of 60 to 90 mg. per 100 cc. for normal blood.

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TOXIC NECROSIS OF THE LIVER DUE TO CINCHOPHEN: REPORT OF FIVE CASES*

SINCE its introduction in 1908 cinchophen, or atophan (phenylquinoline-carboxylic acid) has attained great popularity in the treatment of arthritis and neuritis. In the past few years, however, there has appeared an increasing amount of evidence that this popularity is not entirely deserved, and for rather ominous reasons.

In 1923 Worster-Drought¹ described a case of jaundice due to intoxication with cinchophen. Since that time similar cases, many of them fatal, have been reported with a frequency which has become alarming. Larsen² in a recent review of the literature collected 96 instance of "atophan jaundice," to which he added the ninety-seventh, with a mortality of 43.3 per cent. A number of additional cases reported subsequently by other authors, together with the five to be described, bring the total to well over 100.

REPORT OF CASES

Case I.—A housewife, aged forty-two, was brought to the hospital March 15, 1931, deeply jaundiced and in coma. One sister recently had been confined to another hospital with painless jaundice of two weeks' duration, and one brother had had jaundice for a few days at the age of seven. There was no history of exposure to alcohol, phosphorus or dyes. The husband gave the information that the patient had suffered for ten years from "bilious attacks" accompanied by discomfort under the right costal margin, nausea, belching and gas. About

* This paper was read in part before one of the clinical sessions of the American College of Physicians at Chicago, April 20, 1934.

eating because of a feeling of fulness which followed the ingestion of even small amounts of food.

The temperature was 98° F., pulse 104, and respirations were 20. There was definite jaundice and the sclerae were icteric. The lungs were clear. A soft systolic murmur was heard over the base of the heart. Blood pressure was 168/70. The peripheral vessels were slightly thickened and a water-hammer pulse was noted at the wrist. The abdomen was enormously swollen, with evidence of ascites and edema of the lower abdominal wall. Deep pressure in the epigastrium produced moderate tenderness. The liver and spleen were not palpated. There was slight pitting edema of the dependent parts of the forearms and marked edema of the entire lower extremities.

The erythrocytes numbered 5,000,000, and the leukocytes 9200 to 14,900 per cubic millimeter, with a hemoglobin concentration of 75 per cent. The Wassermann and Kahn tests were negative. The erythrocyte fragility test showed hemolysis beginning at 0.425 per cent sodium chloride solution and complete at 0.275 per cent. The urine contained no albumin and no bile, but a large excess of urobilinogen. The test for occult blood in the stools was 1 to 3 plus. The blood sugar was 75 to 100 mg. and the blood urea nitrogen 17.4 mg. per 100 cc.

August 24th abdominal paracentesis yielded 6000 cc. of a yellow fluid with low specific gravity. A galactose tolerance test of liver function showed an excretion of 3.96 Gm. in five hours (normal, less than 3 Gm.). The bromsulphalein test showed a retention of 100 per cent in one hour. The patient lost her appetite, became disoriented, and sank into stupor on August 31st. The pulse mounted to 120. She remained in a semistuporous state until September 11th, when the temperature rose to 102° F. and she complained of pain in the chest. Examination showed fine râles at the bases of both lungs. The pulse became more rapid and poor in quality. September 12th, the patient lapsed into coma and the respirations became rapid and shallow. Death occurred on September 13th apparently from circulatory failure.

not found again. March 17th, the blood urea nitrogen was 7.5 mg. per 100 cc. The coma deepened, the pulse mounted, edema of the eyelids developed and after a series of convulsions with a terminal rise of temperature, death occurred March 18th.

Autopsy revealed an acute, diffuse toxic necrosis of the liver with marked atrophy (830 Gm.), severe generalized icterus, acute pulmonary edema, absorption atelectasis of the posterior half of the right lower lobe, and slight hyperplasia of the spleen. The gallbladder was normal and contained a few cubic centimeters of black, viscid bile.

Summary.—A housewife of forty-two, with a history of vague upper abdominal distress of ten years' duration, died deeply jaundiced and in coma about six months after she had begun to take large doses of "atophan" for arthritis. She had also taken 20 to 30 grains (1.3 to 2 Gm.) of aspirin daily but had used neither of these drugs recently. Autopsy showed a toxic necrosis and atrophy of the liver (830 Gm.) and a normal gallbladder.

Case II.—A housewife, aged sixty, entered the hospital August 21, 1931, complaining of jaundice and bloating of six weeks' duration.

March 20, 1931, she had been given "atophan" by a doctor for arthritis. She took seventeen $7\frac{1}{2}$ -grain (0.5 Gm.) tablets (127.5 grains (8.5 Gm.) in all) over an unknown period of time. The latter part of June she had an attack of nausea and vomiting lasting several days. About July 4th she noticed a yellow color of the eyes and skin. The jaundice became more marked, then subsided noticeably for a time, but began to increase again about two weeks before admission. With the original onset of jaundice the patient had observed a feeling of fulness and bloating in the abdomen with but little belching and no pain. About August 7th, with the exacerbation of jaundice, the abdomen began to enlarge progressively. For the past week she had had clay-colored stools, lower abdominal pain, edema of the feet and legs, and considerable difficulty in

jaundice progressed steadily and the patient observed that her stools had become increasingly light and the urine increasingly dark in color. There was no history of exposure to cold and the patient had had no abdominal pain, chills, fever or headache. She was a total abstainer from alcohol and had been in contact with no other toxic substances.

On physical examination the temperature was found to be 99.2° F., pulse 100 and respirations 22. There was a generalized, pumpkin-yellow jaundice. Hepatic dulness was reduced to about one half its normal extent. There was a 6-inch scar with a draining sinus on the anterolateral aspect of the right thigh and a complete ankylosis of the right hip. The heart and lungs showed no abnormality. The blood pressure was not taken. The spleen was not palpated and there was no evidence of ascites.

There were 3,750,000 erythrocytes and 8200 to 13,200 leukocytes per cubic millimeter with a hemoglobin value of 55 per cent. The urine was strongly positive for bile and contained a trace to a large excess of urobilinogen; albumin was absent and leucine and tyrosine crystals were not found. The stools contained bile and were negative for blood. The galactose tolerance test showed an excretion of 5 Gm., and the retention of bromsulphalein in the blood stream was 100 per cent at the end of an hour. The blood sugar was 71 and the blood urea nitrogen 5.7 mg. per 100 cc.

The pulse soon rose to a high level, ranging from 120 to 140 or more throughout the course of the disease with but little elevation of temperature. The patient was nauseated and ate with difficulty. On February 23rd she vomited and the excretion of urine became much diminished. Examination revealed shifting dulness in the abdomen, an area of liver dulness only 3 cm. in width and beginning edema of the legs. Intravenous dextrose therapy, which had been started soon after admission, was now reinforced by the administration of insulin. The next day the patient was mentally sluggish. A definite fluid wave was obtained in the abdomen. The jaundice became deeper and urobilinogen disappeared from the urine.

The autopsy findings consisted of generalized icterus, regenerating toxic necrosis of the liver with atrophy (820 Gm.) and beginning cirrhosis, marked ascites, hyperplasia of the spleen, slight bilateral hydrothorax, moderate cardiac enlargement (525 Gm.) with slight passive congestion of the lungs and spleen, focal areas of fat necrosis about the pancreas and edema of the large bowel, especially in the region of the cecum. Analysis of a specimen of liver showed a glycogen content of less than 0.3 per cent (normal, about 5 per cent).

Summary.—A sixty year old housewife developed jaundice and ascites three and one-half and four and one-half months respectively after her physician had first given her "atophan" for arthritis. She had taken 127.5 grains (8.5 Gm.) over an unknown period of time. Death occurred in coma. Autopsy revealed a regenerating toxic necrosis and atrophy of the liver (820 Gm.) with beginning cirrhosis.

Case III.*—A female school teacher, aged fifty, entered the hospital February 17, 1933, complaining of jaundice of two weeks' duration. She had sustained a fracture of the right femur in 1926 which had necessitated several operative procedures. In August, 1932, an antrum window was made for chronic empyema of a maxillary sinus. Early in the fall of 1932 she had taken "a few" tablets of "atophan" prescribed by her doctor for the relief of rheumatic pains. In December, 1932, the arthritis became worse following a cold and on her own initiative the patient had the prescription refilled three times. Between December 22, 1932, and January 6, 1933, she took twenty-four to thirty $7\frac{1}{2}$ -grain (0.5 Gm.) tablets (180 to 225 grains (12 to 15 Gm.) in all) of "atophan." In January, 1933, tonsillectomy was performed under local anesthesia. About February 3, 1933, the patient's friends noticed that she was jaundiced. Two days later she had an episode of nausea and vomiting which was repeated on February 13th. Between February 3rd and February 17th (the date of admission) the

* This case is to be reported elsewhere from a slightly different angle by Dr. Theodore E. Heinz.

stiff neck followed by severe "neuritis," for which her doctor prescribed "farastan" (a preparation of monoiodo-cinchophen). She took twenty to twenty-four 3-grain (0.2 Gm.) capsules (60 to 72 grains (4 to 4.8 Gm.) in all) in one month. During February and most of March, 1933, the patient felt quite well. March 21st, six days before admission, she noticed jaundice which became progressively more marked. Neither before the jaundice nor during its early course had there been any respiratory infection, fever, headache, nausea, vomiting, diarrhea, pain or pruritus.

The temperature was 97.5° F., pulse 88 and respirations were 20. The skin showed a deep golden-yellow tint and the sclerae were icteric. Acne vulgaris was present on the face. One of the right submaxillary lymph nodes was enlarged. The heart and lungs were normal. Blood pressure was 96/60. The abdomen was flat with no evidence of fluid. The upper border of liver dulness was found in the fifth interspace, and a soft, smooth edge was felt 4 cm. below the costal margin in the right mammary line on deep inspiration. The spleen was not palpable or enlarged to percussion.

The erythrocytes numbered 4,500,000 and the leukocytes 7000 per cubic millimeter. The hemoglobin concentration was 74 per cent. The blood Wassermann and Kahn were negative. The urine at first was strongly positive for bile but later became negative. Urobilinogen was present in small traces on admission, in excess about the middle of the patient's course, and in normal amounts at discharge. Tests of liver function yielded the following results:

Date.	Bromsulphalein retention, per cent.		Grams of galactose excreted in 5 hours.
	One-half hour.	One hour.	
(Normal).....	10-20	0	less than 3
March 27.....	100	100*	
March 28.....	2.95
April 4.....	7.04
April 6.....	100	100*	
April 8.....	3.71
April 11.....	...	50†	2.00

* Dosage of 5 mg. per kilogram of body weight.

† Dosage of 2 mg. per kilogram of body weight.

The blood urea nitrogen dropped to 3.7 mg. and the amino acid nitrogen to 5.6 mg. per 100 cc. (normal, 6 to 8).

February 25th, fifteen minutes after she had been given dextrose and insulin, she was seized with severe pain which she was unable to localize, became pale and gasped for breath. The pulse was imperceptible. She rallied in a few minutes but respirations continued labored for an hour. On this day the stools were found strongly positive for occult blood. February 27th, the patient was nauseated and retching, vomited coffee-ground material, and began to cough. Oliguria recurred and edema of the legs became marked. The blood sugar fell to 53 mg. per cent and the plasma proteins to 5.5 Gm. per 100 cc. with an albumin-globulin ratio of 0.32. Death occurred March 4th after three days of coma, urinary incontinence and generalized anasarca.

At autopsy the principal findings were marked icterus, edema of the dependent parts of the body, toxic cirrhosis of the liver with moderate atrophy (600 Gm.), ascites, atrophy of the spleen, icteric nephrosis, multiple petechial hemorrhages of the gastro-intestinal mucosa, and multiple superficial hemorrhagic ulcers of the duodenum. There was no amyloidosis.

Summary.—A female school teacher of fifty complained of jaundice, nausea and vomiting which had begun four weeks after taking the last of a total of 180 to 225 grains (12 to 15 Gm.) of "atophan" over a period of two weeks. The jaundice deepened, ascites and edema appeared, hemorrhage occurred into the gastro-intestinal tract and the patient died in coma. Toxic cirrhosis and atrophy of the liver (600 Gm.) and multiple ulcers of the duodenum were found at autopsy.

Case IV.—An unmarried woman of thirty-seven entered the hospital March 27, 1933, complaining of a skin eruption of five months' duration and progressive jaundice for one week. In October, 1932, nonitching, noninflammatory lesions had appeared on the face. A doctor gave her a cathartic which she thought contained iron and which she had continued to take to date. In December, 1932, the patient developed a cold and a

On physical examination the temperature was 99.2° F., pulse 92, and respirations 24. The patient was well oriented. The skin was dry, thin and wrinkled and of a definitely icteric color. The lungs were normal and the heart tones distant. Blood pressure was 166/95. The abdomen was large and distended, with dulness in both flanks suggestive of fluid. Liver dulness extended to the right costal margin but the edge was not felt. The spleen was not palpated. There were findings indicative of a fracture of the neck of the left femur.

The erythrocyte count was 5,020,000, the leukocyte count 10,600 and the hemoglobin 90 per cent. Blood Wassermann and Kahn tests were negative. The urine showed a trace of bile on two occasions. No test for urobilinogen was made.

May 19th the fracture was reduced by closed manipulation under nitrous oxide and oxygen analgesia of one hour's duration, and a cast was applied. During the rest of the day the patient remained drowsy and was unable to void. For the next few days her appetite was poor and she had a continuous sensation of fulness in the epigastrium. There was no apparent change in the jaundice. May 26th edema of the right lower leg was observed. May 27th two large hematemeses occurred, followed by a third on the following day, and alkali therapy by mouth was begun. May 29th the patient lapsed rather suddenly into coma. The pulse was of poor quality but the rate was not elevated nor was the blood pressure materially lowered. Chemical determinations on that day showed a blood urea nitrogen of 47.2 and a blood sugar of 115 mg. per 100 cc. and plasma proteins of 4.1 Gm. per cent. May 30th the patient died with many coarse râles in the chest.

Autopsy revealed slight icterus, subacute toxic necrosis of the liver with focal regenerative hyperplasia, early cirrhosis and fatty changes (weight, 650 Gm.), ascites, multiple acute erosions of the lower esophagus, dilatation and necrosis of the esophageal veins with recent hemorrhage into the gastro-intestinal tract, focal acute pancreatitis with peripancreatic fat necrosis, moderate bilateral hydrothorax and pulmonary edema, hemorrhagic tracheobronchitis, recent subendocardial hemor-

Treatment consisted of a high carbohydrate diet, forcing of fluids and phenobarbital as a sedative. As a means of raising the carbohydrate intake, fruit juice and lactose were given in large quantities. For the first few days the patient experienced mild epigastric distress and a feeling of fulness and nausea but did not vomit. Gradually the jaundice subsided and she was discharged after seventeen days in the hospital. She was seen three weeks later in the out-patient department where she complained of fatigue, constipation, and continued pain in the back and neck. The jaundice had cleared entirely and the liver and spleen were not palpable.

Summary.—An unmarried woman of thirty-seven had taken a total of 60 to 72 grains (4 to 4.8 Gm.) of "farastan," prescribed by her physician, over a month's time. About seven weeks after taking the last capsule she became jaundiced and later experienced a sensation of epigastric fulness and nausea. The liver was enlarged and the stools contained occult blood on one occasion. The patient improved on a high carbohydrate diet and was discharged from the hospital twenty-three days after the onset of jaundice.

Case V.—A woman of seventy-five was admitted to the hospital May 17, 1933, for fracture of the left femur. Jaundice, unsuspected by the patient, was noted by the examining physician. The patient stated that she had been subject to "rheumatism" for many years. Two months before admission she began taking cinchophen on her own initiative. About the same time her appetite fell off markedly and she "felt very full" after eating only a small meal. These symptoms subsided and she continued to take cinchophen, three tablets daily, for the first two weeks and then two or three per day irregularly, sometimes going for several days without any. She took slightly over 100 tablets in the two months preceding admission, with considerable relief from her arthritis. For four or five days before her accident she had severe, generalized abdominal pain and distention with clammy perspiration and mild nausea but no vomiting. She did not use alcohol and no history of exposure to other toxins was obtained.

nosis of catarrhal jaundice, the etiology of which is unknown, would not be justified. As a matter of fact, the clinical similarity of these two conditions is not surprising in the light of the modern conception of the pathology of acute catarrhal jaundice,^{3, 4} which has been described as "an acute yellow atrophy in miniature."⁵ The enlargement of the liver in this case does not militate against the diagnosis of cinchophen poisoning, for the same finding was noted in Case I before the patient was admitted to the hospital, and has been observed frequently in the initial stages of toxic hepatitis from other causes.

In Cases II, III and V toxic necrosis of the liver followed the ingestion of cinchophen by patients who gave no evidence of previous hepatic injury and in whose histories no other etiologic factor could be elicited.

The earlier symptoms of cinchophen poisoning as illustrated by these patients were either jaundice or gastro-intestinal disturbances, including flatulence, a feeling of fulness after meals, vague epigastric distress, anorexia, nausea and vomiting. Clay-colored stools and dark urine were observed by three patients. Diarrhea did not occur. Later, in the fatal cases, edema appeared in two instances. In three of the five patients there was bleeding into the gastro-intestinal tract as evidenced either by the presence of occult blood in the stools on a meat-free diet or by gross hematemesis. A characteristic feature in all the fatal cases was marked drowsiness which increased with the deepening jaundice and passed sooner or later into coma with or without the intervention of active delirium. Death occurred quietly in most of the patients, apparently from circulatory failure, but was preceded in Case I by convulsions.

Physical examination revealed three striking and typical findings: First, in all the acute cases, a golden- or pumpkin-yellow jaundice quite distinct from the greenish-yellow color produced by continued mechanical obstruction of the bile passages; second, in two of the fatal cases, a progressive diminution in the area of liver dulness which was shown at autopsy

rhage and hemorrhage into an atheromatous aortic plaque with rupture of the media, infected hemorrhagic uterine polyp, uterine fibroleiomyoma and a bloody vaginal discharge.

Summary.—Jaundice was observed by the examining intern upon the admission of a seventy-five year old woman for fracture of the femur. In the preceding two months the patient on her own initiative had taken over 100 tablets, presumably $7\frac{1}{2}$ grains (0.5 Gm.) each, of cinchophen (a total of over 750 (?) grains (50 Gm.)) for arthritis. She had three massive gastric hemorrhages and died two days later in coma. Autopsy revealed toxic necrosis, atrophy and cirrhosis of the liver (650 Gm.) with dilated and necrotic esophageal veins and numerous scattered hemorrhagic manifestations.

DISCUSSION

The question of whether cinchophen was actually responsible for the symptoms exhibited by these patients must, it would seem, be answered in the affirmative. The patient in Case I, it is true, had had for ten years symptoms which might be interpreted as pointing to disease of the gallbladder, liver or other parts of the gastro-intestinal tract, and gave a history, though unreliable, of possible enlargement of the liver five or six years previously. The clinical course of the jaundice, however, and especially the autopsy findings leave no doubt that this patient was suffering from an acute toxic hepatitis. There was no pathologic evidence of an old or recent cholecystitis. The negative rôle played by aspirin in doses of 20 to 30 grains daily needs no comment. The known absence of other etiologic agents and the fact that the patient had taken cinchophen in large doses cannot but incriminate this drug. The family history of jaundice in one brother at the age of seven and in one grown sister recently is of interest and possibly of significance.

The patient in Case IV ran a course which would be compatible with a severe catarrhal jaundice except for the absence of the usual premonitory gastro-intestinal disturbances. In the face of a history of cinchophen ingestion, however, a diag-

dropped from 71 mg. soon after admission to 53 mg. a week before death. This phenomenon is in accord with the facts established by Mann,⁷ that the liver is the immediate source of blood sugar in the body and that this substance is reduced to very low levels after hepatectomy.

The necropsy findings in these cases correspond to the usual descriptions of acute and subacute toxic necrosis of the liver, the most recent account of which has been given by Permar and Goehring.⁸ Cirrhotic changes were observed in three instances, and in one case multiple ulcers of the duodenum were present.

The incidence of cinchophen poisoning among cases of acute yellow atrophy has, in our experience, been high. Of six patients who have died of toxic necrosis of the liver in the Billings Hospital since 1931, four gave a history of having taken cinchophen in one form or another, whereas in only two cases was the etiology obscure. The fact that such a large proportion of cinchophen-positive histories was obtained in one hospital over a period of two and a half years suggests that this drug more frequently plays a rôle in the production of acute yellow atrophy than is commonly suspected, and that such cases would be found to be more numerous if the possibility of cinchophen poisoning were kept more constantly in mind.

Of the five cases presented in this report, four terminated fatally. It so happens that the only patient who recovered had taken "farastan" (monoiodo-cinchophen) instead of the pure preparation, and had taken somewhat smaller amounts than the patients who died. This, however, is only fortuitous, for fatal results have been observed to follow the use of "farastan,"⁹ and jaundice has occurred from much smaller doses of cinchophen.¹⁰

What determines whether a given patient under cinchophen treatment will tolerate it well or will respond by exhibiting toxic symptoms? This question never has been answered satisfactorily. It cannot be a matter of total dosage, for we have the record of one patient who took 40 to 90 grains (2.6 to 6 Gm.) daily over a period of eighteen years apparently

to be due not only to an actual decrease in the size of the liver but also to a falling away of the organ from the anterior wall of the chest; and third, particularly in the severe cases, a consistent elevation of the pulse line above the temperature line.

Tests of liver function performed in three cases yielded evidence of marked impairment by both the bromsulphalein and the galactose methods, but they were of little practical value in diagnosis and prognosis. There was no correlation of the outcome of the tests with the severity of the disease as between individuals, for the patient (Case IV) whose tests showed the greatest abnormality was the only patient who recovered. It is possible that had the condition of the other two patients permitted a repetition of some of the tests as the disease progressed this discrepancy would not have appeared. The patient in Case IV, indeed, did exhibit a close parallelism between her clinical improvement and the improvement in the galactose tolerance test. The marked derangement of hepatic function as determined by the special tests described was borne out by the presence of a large excess of urobilinogen in the urine. This substance was absent in Case I, the patient having been admitted almost in extremis, and disappeared terminally in Case III, probably because bile was no longer reaching the intestine, although this was not checked by examination of the stools.

In Cases I, III, and IV the blood urea nitrogen was found to be as low as 7.5, 3.7 and 4.7 mg. per 100 cc. respectively. Since the liver is known to be the site of urea formation, it is not surprising that severe hepatic insufficiency is sometimes accompanied by decreased concentrations of urea in the blood. The lowest value observed was in a patient who nevertheless had an oliguria and, as discovered at autopsy, an icteric nephrosis. A similar case was reported by Rabinowitch⁶ in 1929. Why the concentration of this substance was normal or increased in Cases II and V is not clear.

Another interesting feature of abnormal hepatic physiology is brought out in Case II, in which, despite repeated intravenous infusions of dextrose solution, the blood sugar fell to 31 mg. per cent two days before death. In Case III the blood sugar

short of the mark. None of the patients in this series had early skin manifestations. As for gastro-intestinal symptoms, it is true that in Cases II and V they preceded the onset of icterus, and if the drug had been discontinued promptly death might have been averted. In the three remaining cases, however, nausea, vomiting, epigastric distress and flatulence did not put in an appearance until after the drug had been stopped, and yet so much hepatic tissue already had been destroyed that jaundice occurred, followed by coma and death in two of the three cases. Such symptoms therefore constitute a false and unreliable standard for gaging the dosage of cinchophen. With respect to jaundice, the fact is that in many cases the onset of icterus marks the beginning of the end, and in other cases, including at least three of this series, the patient had stopped taking the drug weeks or even months before jaundice appears. Cinchophen apparently sets up in the livers of certain individuals an irreversible pathologic process which progresses long after the withdrawal of the drug and which, in spite of the regeneration of considerable hepatic tissue, may lead to the death of the patient. Jaundice, then, as guide to therapy, is not only valueless but dangerous, for by the time it makes its appearance irreparable damage may have been done.

There is, in brief, no dependable symptomatic sign-post to warn either patient or physician of impending toxicity in time to prevent possible disaster.

When it is realized that cases of cinchophen poisoning are being reported with increasing frequency, that reliable criteria of sensitivity do not exist, that toxic symptoms often appear too late to be of value as a therapeutic guide, and that in many severe cases we are totally unable to prevent a fatal termination, the dangers attendant upon the use of this drug should become obvious. That such cases continue to be reported, however, suggests that these dangers are not fully appreciated. The foregoing considerations, together with the fact that improperly labelled preparations containing cinchophen can be bought without prescription over the counter of any drug store,

with impunity,¹¹ whereas vomiting and jaundice were produced in Evans'¹⁰ patient after the ingestion of only 15 grains (1 Gm.). The amounts taken by most of the patients in this series were not excessive, yet the mortality was 80 per cent.

As is true in many of the fields of medicine, we are probably concerned here with a balance between the potency of the disease-producing agent and the resistance or susceptibility of the individual. The paradox of dosage has led many investigators to fall back on the sensitivity of the particular patient as the determining factor in the intolerance of persons to cinchophen. Proof that this mechanism is involved in at least some instances has been furnished by Scully¹² who reported anaphylactoid reactions following a single dose. Short and Bauer¹³ have recently described four cases of allergic reaction due to cinchophen and its derivatives and have collected thirty-seven others from the literature. Various authors have advanced the theory that patients in whom cinchophen produces hepatic manifestations either have an innate or acquired idiosyncrasy for the drug or have suffered previously from diseases such as cholecystitis, cirrhosis, catarrhal jaundice, alcoholism or other toxicoses which render the liver sensitive to this added insult. It should be noted that in our Cases II, III, IV and V no history suggesting earlier hepatic damage could be obtained.

In view of the untoward results which are sometimes produced by cinchophen therapy, two questions naturally present themselves: First, is there any way of determining in advance whether a patient will react unfavorably? And second, what are the symptoms that indicate beginning toxicity?

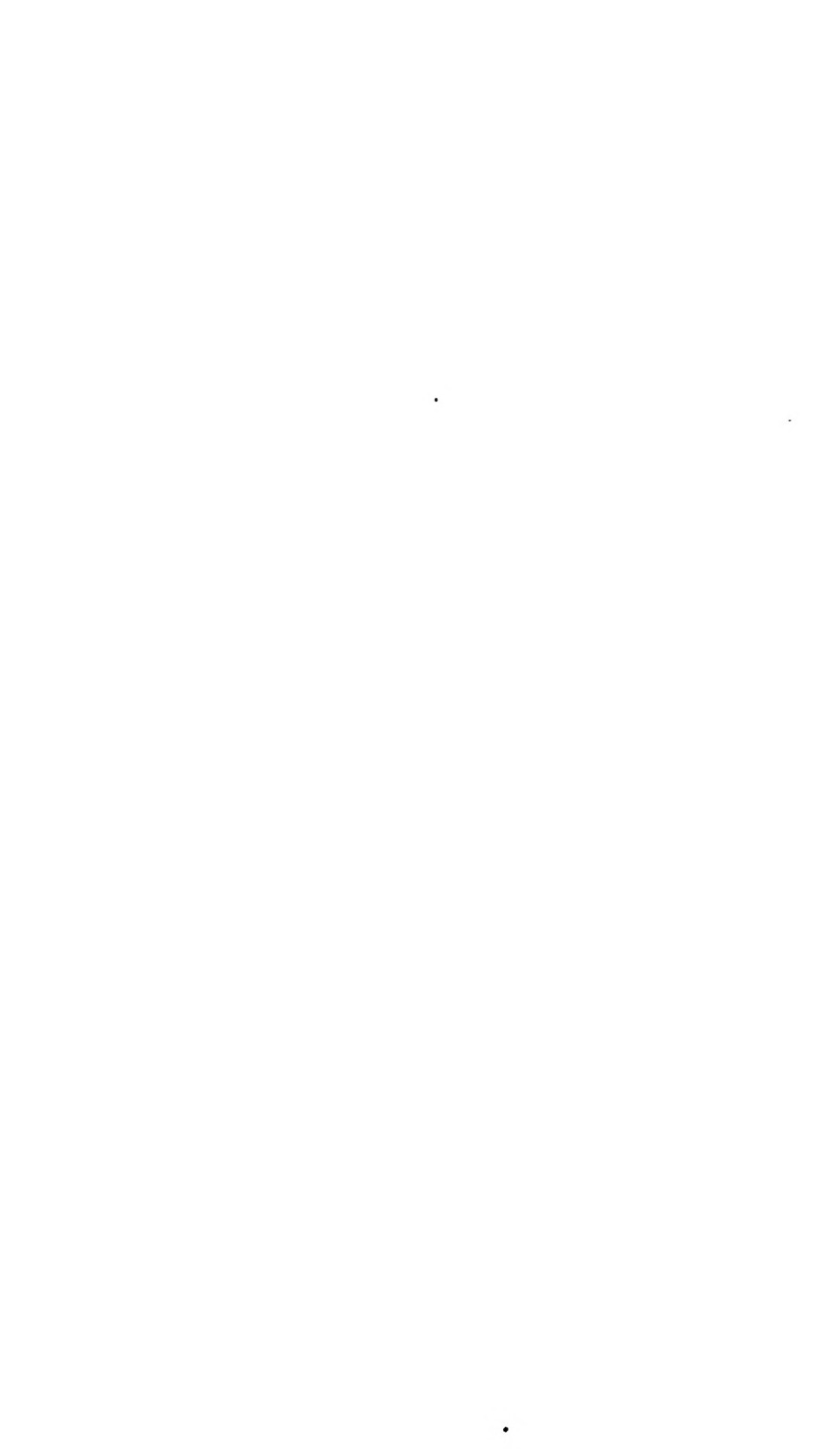
In answer to the first question, there is to my knowledge no dependable test of cinchophen sensitivity except that of the actual introduction of the drug into the body. Skin tests are of no value.

In answer to the second question, the statement is often made that if skin reactions, gastro-intestinal disturbances or jaundice supervene during a course of treatment, medication should be discontinued at once. This obvious warning stops

raise once more the pertinent question as to the advisability of retaining cinchophen and its compounds in our therapeutic armamentarium.

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